Clear cell urothelial carcinoma of the urinary bladder - a rare pathological entity. A case report and a systematic review of the literature

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ABSTRACT

The most common histological type of urinary bladder cancer is urothelial carcinoma (UC). In contrast, the clear cell variant of urothelial carcinoma (CCUC) is quite a rare neoplasm. In this study, we report a case of an 81-year-old male, presenting with gross hematuria and acute urinary retention, which was subsequently diagnosed with CCUC at our pathology department. Furthermore, we provide a short systematic review of the literature (PubMed, Scopus, and Science Citation Index) for this rare histopathological entity and a brief discussion about its morphological and immunohistochemical (IHC) characteristics.

KEY WORDS: Clear cell urothelial carcinoma; urinary bladder; review

DOI: http://dx.doi.org/10.17305/bjbms.2019.4182 *Bosn J Basic Med Sci. xxxx;xx(x):1-4.*

INTRODUCTION

Cancer affecting the urinary bladder is a prevailing disease worldwide, with epidemiological studies reporting its incidence at 541,000 cases per year globally, and approximately 150,000 deaths per year [1]. The most common histological types of bladder cancer - urothelial carcinoma (UC) and its ten different variants recognized by WHO [2], squamous cell carcinomas, adenocarcinomas, and undifferentiated carcinomas [2] have been extensively described. In contrast, clear cell urothelial carcinoma (CCUC) of the urinary bladder is a rare neoplasm; to our knowledge, with only 13 cases reported in the literature [3-13], including our case at the time of this review.

CASE REPORT

An 81-year-old male presented to our hospital with gross hematuria and acute urinary retention. Computed tomography (CT) scan revealed an 7.5/7/4 cm exophytic mass arising on the posterosuperior aspect of the urinary bladder, extending beyond the bladder wall, infiltrating the perivesical fat with no evidence of metastasis. Transurethral resection of the urinary bladder tumor (TURBT) was performed, a diagnosis of CCUC was established, and a radical cystoprostatectomy was decided.

The gross examination of the resection specimen revealed a large and hemorrhagic exophytic urinary bladder mass involving the posterior wall and extending to the dome of the bladder, invading the perivesical adipose tissue (Figure 1).

Microscopic examination of the tumor revealed sheets of polygonal cells with abundant clear cytoplasm (>95% clear cell differentiation), marked nuclear pleomorphism, and low mitotic activity (Figure 2A), while 5% of tumor showed features of high-grade urothelial carcinoma. No glandular/tubular differentiation and no hobnail cells were observed. Large areas of tumor necrosis were present with scant calcifications. The microscopic evaluation confirmed the infiltration of the perivesical adipose tissue. Perineural invasion and vascular invasion were also noted. Urothelial carcinoma *in situ* (CIS) was identified in both ureters. The evaluation of the regional lymph nodes showed metastatic deposits of infiltrating CCUC in 4 out of the 11 lymph nodes examined.

To establish the underlying substrate of clear, vacuolated cytoplasm of the tumor cells histochemical staining was

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Submitted: 06 March 2019/Accepted: 23 March 2019

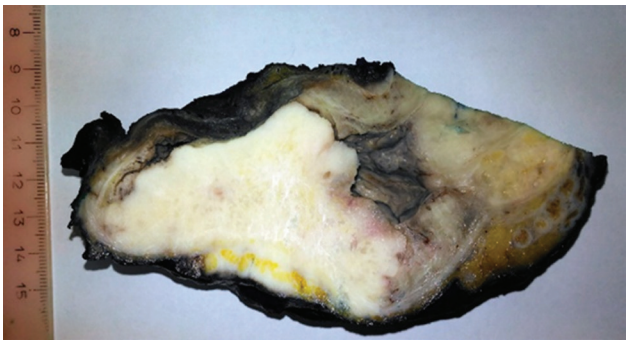

FIGURE 1. Gross aspect of the cystoprostatectomy specimen. Invasion through the detrusor muscle into the perivesical adipose tissue.

performed. The tumor cells were focally positive for periodic acid-Schiff [PAS] (Figure 2B) and negative after the diastase (PAS-D) treatment. The immunohistochemical (IHC) analysis showed the following profile of the tumor cells: extensive positive reaction for cytokeratin 7 (CK7), GATA-3 (Figure 2C), p63 (Figure 2D), CK5 (Figure 2E), epithelial membrane antigen (EMA), and CK34βE12; a focal positive reaction for CD44 (Figure 2F) and cancer antigen 125 (CA-125); and a negative reaction for CK20, paired box gene 8 (PAX8), renal cell carcinoma marker (RCC Ma), vimentin, S100 protein, HMB45, placental alkaline phosphatase (PLAP), and prostate-specific

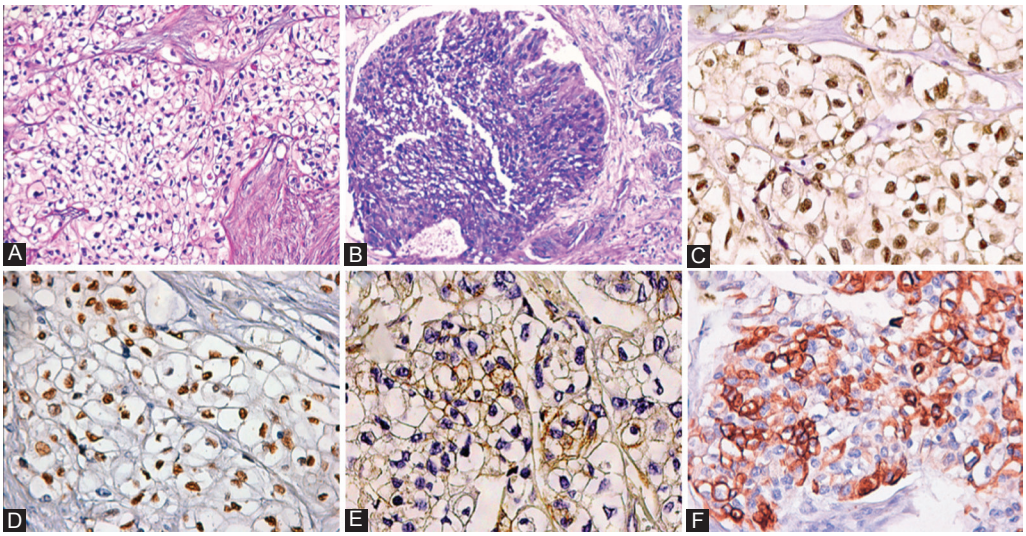

FIGURE 2. (A) Sheets of clear cells invading the muscularis propria, hematoxylin and eosin (HE), ×200. (B) Periodic acid-Schiff (PAS) staining demonstrating glycogen content of the tumor cells, ×200. (C-F) Positive reaction for GATA3, p63, CD44, and cytokeratin 5, ×400.

TABLE 1. IHC and special histochemical staining data

Antibody	Reactivity	Company	Clone	Dilution
CK7	>90%, membranous and cytoplasmic	Novocasta	RN7	RTU
p63	20%, nuclear	Dako	DAK-p63	1:300
CK5	>20%, membranous	Novocasta	XM26	RTU
GATA3	>90%, nuclear	Cell Marque	L50-823	RTU
CA-125	10%, membranous	Novocasta	Ov185:1	RTU
HMWCK	>90%, membranous	Menarini Diagnostics	34betaE12	RTU
EMA	70%, membranous and cytoplasmic	Cell Marque	E29	RTU
CD44	30%, membranous	Cell Marque	MRQ-13	RTU
CK20	Negative	Novocasta	Ks20.8	RTU
PAX8	Negative	Immunologic	ILQ-150	1:200
RCC	Negative	Dako	SPM314	1:50
Vimentin	Negative	Immunologic	V9	RTU
S100	Negative	Novocasta	Polyclonal	RTU
HMB45	Negative	Novocasta	HMB45	RTU
PLAP	Negative	Dako	8A9	RTU
PSA	Negative	Dako	Polyclonal	RTU
Histochemical stain				
PAS	Positive, cytoplasmic	Manual	-	-
PAS-diastase	Negative	Manual	-	-

RTU: Ready to use; IHC: Immunohistochemical; CK: Cytokeratin; CA-125: Carcinoma antigen 125; HMWCK: High molecular weight cytokeratin; EMA: Epithelial membrane antigen; PSA: Prostate-specific antigen; PLAP: Placental alkaline phosphatase; RCC: Renal cell carcinoma; PAS: Periodic acid-Schiff

TABLE 2. Outline of reported cases of clear cell variant of urothelial bladder carcinoma

Reference	Number of patients	Gender	Age	Symptoms	Tumor location	Staging	Treatment	Outcome/Follow-up/ prognosis
Kotliar et al. [3]	1	Male	71	Painless gross hematuria	Left lateral wall involvement into perivesical fat	pT3	Radical cystectomy and adjuvant chemotherapy	Death after 20 months
Braslis et al. [4]	1	Male	70	Frequency, urgency, anuria	No data available	pT2	Radical cystectomy	No data available
Yamashita et al. [5]	1	Male	70	Asymptomatic hematuria	Left lateral wall	pT2	Transurethral resection of the urinary bladder tumor (TURBT)	No recurrence after 7 months on follow-up
Isono et al. [6]	1	Female	69	Gross hematuria	Right lateral wall	No data available	TURBT	No recurrence after 20 months
Rotellini et al. [7]	1	Male	82	Asymptomatic	No data available	pT2	Radical cystectomy	Alive at 12 months
Persec et al. [8]	1	Male	72	Painless macroscopic hematuria	Left lateral wall	No data available	TURBT	No data available
Kramer et al. [9]	1	Male	67	Lower urinary tract symptoms	Trigone	pT4	Radical cystectomy	Death after 14 weeks
Klimis et al. [10]	1	Male	78	Asymptomatic gross hematuria	Right latero-superior wall	pT2	TURBT	No recurrence after 6 months on follow-up
Knez et al. [11]	1	Male	75	Intermittent hematuria	Inferior right lateral wall	pT3b	Radical cystectomy	No recurrence after 12 months on follow-up
Zhang et al. [12]	1	Male	65	Intermittent gross hematuria and dysuria	Left, anterior and posterior wall	No data available	TURBT and adjuvant chemotherapy	Alive at 15 months
Mai et al. [13]	1	Male	75	Hematuria	Left, lateral/trigone	pT3	Radical cystectomy	Alive with no evidence of disease at 2 years
	1	Male	55	Hematuria	Floor	pT3	Radical cystectomy	Alive with no evidence of disease at 2 years
Our case	1	Male	81	Gross hematuria	Posterior-superior wall	pT3b	Radical cystectomy	Death after 5 months

antigen [PSA] (Table 1). Based on histological features and IHC profile, the diagnosis of urothelial carcinoma with clear cell differentiation was established. Shortly after, the patient developed bone metastases, and he died 5 months after the diagnosis.

DISCUSSION

The CCUC affecting the urinary bladder is a rather new and sporadic diagnosis encountered in the pathology of urinary tract tumors. Limited reports have been made since 1995 when it was first described by Kotliar et al. [3] as a recognizable variant of urothelial carcinoma. Frequently, clear cell components are encountered in UC; however, Knez et al. [11] were the first to use a cut-off percentage (~90%) of clear cells to differentiate CCUC. Due to the limited knowledge regarding CCUC, as a pathologic entity and its prognosis, the true incidence of CCUC is uncertain. However, a three-fold increase in published cases is observed starting from 2010. This can be due to an increase in IHC use, more reliable antibodies, better scientific communication, and a better understanding of the pathology of bladder tumors.

Based on the 13 reported cases in the literature, including our case, a clear predisposition toward male sex is found (male: female – 12:1), with a mean age at diagnosis of 71.5 years (range, 55–82) [3-13]. At initial presentation, gross hematuria is the most frequently encountered symptom (10 cases) [3,5,6,8,10-13]. Among the 13 documented cases, tumor extension was provided for 9 cases [3-5,7,9-11,13] while for 3 cases no data was available [6,8,12]; thereafter 4 cases were pT2, 5 cases pT3, and 1 case was pT4. Only 7 cases had undergone radical removal of the urinary bladder [3,4,7,9,11,13]. Of the 13 cases, 3 patients died (with a mean survival of 9.5 months) [3,9], 8 patients were alive at follow-up (with a mean follow-up period of 16 months), and 2 cases had no follow-up data available (Table 2).

Clear cell carcinomas may occur in almost any site, making the differential diagnosis problematic. Taking into consideration that the clear cell tumor was located in the urinary bladder, our first differential diagnosis was with clear cell adenocarcinoma of the urinary bladder. In our case, the tumor presented a solid, sheet-like growth pattern (Figure 2A) and was PAX8 negative. In contrast, clear cell adenocarcinoma is PAX8 positive [11,14-16], and it can have a solid growth pattern with glandular differentiation and tubulocystic or papillary morphology, with or without hobnail cells [2,16]. Based on the negative reaction of the tumor cells for RCC, HMB-45/S-100, PSA, PLAP, and vimentin, secondary involvement of the urinary bladder by clear cell carcinoma of the kidney, melanoma, prostate cancer, seminoma, or by clear cell sarcoma was excluded. Aspects which were confirmed by whole-body CT – scan results. Moreover, the presence of high-grade

urothelial carcinoma and CIS favored the diagnosis of a primary tumor.

The tumor cells were focally positive for PAS (Figure 2B), confirming the presence of cytoplasmic polysaccharides, such as glycogen, and not mucin or lipids. Regarding this aspect, Kotliar et al. [3] suggested that the loss or the focal positivity for PAS/PAS-D could be correlated with the tumor grade, more precisely with a poorly differentiated, aggressive tumor, a feature that was noticed in our case as well.

Mai et al. [13] observed that the expression of basal cell markers CK5 and CD44 in CCUC, indicating a basal-like phenotype of the tumor cells, is consistent with an aggressive behavior. Based on these criteria, our patient fitted the expected outcome, with aggressive and rapid clinical evolution of the disease and the development of bone metastases, followed by death 5 months after the initial diagnosis was established.

CONCLUSION

In conclusion, CCUC is a rare variant of UC; to our knowledge, the present case is the first reported case in Romania. The differential diagnosis with more common malignant primary tumors, as well as metastatic lesions, should be made based on the correlation of histological aspects and histochemical and IHC staining. CCUC has a higher incidence in the elderly (eighth decade of life), typically affects male patients, requires an aggressive treatment, and has a variable outcome.

To properly characterize CCUC as a pathological entity, we need to study in detail more cases. Moreover, tumor behavior needs to be defined, and a uniform therapeutic guideline must be established.

ACKNOWLEDGMENTS

This paper is partially supported by the Project "Multicenter study on the use of a robotic approach in order to correlate a decrease of circulating adipokine level in obesity with the risk of pelvic cancer, <ROBOCAPE>" POSCCE – ID 1846/Code SMIS 48478 – No. 669/01.09.2014.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

[1] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. JAMA Oncol 2017;3(4):524-48. https://doi.org/10.1001/jamaoncol.2016.5688.

[2] Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs-part B: Prostate and bladder tumours. Eur Urol 2016;70(1):106-19. https://doi.org/10.1016/j.eururo.2016.02.028.

[3] Kotliar SN, Wood CG, Schaeffer AJ, Oyasu R. Transitional cell carcinoma exhibiting clear cell features. A differential diagnosis for clear cell adenocarcinoma of the urinary tract. Arch Pathol Lab Med 1995;119(1):79-81.

[4] Braslis KG, Jones A, Murphy D. Clear-cell transitional cell carcinoma. Aust N Z J Surg 1997;67(12):906-8. https://doi.org/10.1111/j.1445-2197.1997.tb07625.x.

[5] Yamashita R, Yamaguchi R, Yuen K, Niwakawa M, Tobisu K. Urothelial carcinoma (clear cell variant) diagnosed with useful immunohistochemistry stain. Int J Urol 2006;13(11):1448-50. https://doi.org/10.1111/j.1442-2042.2006.01569.x.

[6] Isono M, Asano T, Shirotake S, Tasaki S, Asakuma J, Satoh M, et al. Urothelial carcinoma clear cell variant of the urinary bladder: A case report. Hinyokika Kiyo 2010;56(3):163-5.

[7] Rotellini M, Fondi C, Paglierani M, Stomaci N, Raspollini MR. Clear cell carcinoma of the bladder in a patient with a earlier clear cell renal cell carcinoma: A case report with morphologic, immunohistochemical, and cytogenetical analysis. Appl Immunohistochem Mol Morphol 2010;18(4):396-9. https://doi.org/10.1097/PAI.0b013e3181d57dce.

[8] Persec Z, Buković D, Peršec J, Rako D, Ljubanović D, Starčević V, et al. Clear cell variant of urothelial carcinoma in urinary bladder; a clinicopathological and immunohistochemical study a case report. Coll Antropol 2012;36(3):1045-7.

[9] Kramer MW, Abbas M, Pertschy S, Becker JU, Kreipe HH, Kuczyk MA, et al. Clear-cell variant urothelial carcinoma of the bladder: A case report and review of the literature. Rare Tumors 2012;4(4):153-5. https://doi.org/10.4081/rt.2012.e48.

[10] Klimis T, Dellaportas GP. Clear cell variant of urothelial carcinoma. Hell Cheirourgike 2012;84(3):191-4. https://doi.org/10.1007/s13126-012-0023-z.

[11] Knez VM, Barrow W, Lucia MS, Wilson S, La Rosa FG. Clear cell urothelial carcinoma of the urinary bladder: A case report and review of the literature. J Med Case Rep 2014;8(1):275. https://doi.org/10.1186/1752-1947-8-275.

[12] Zhang Y, Huang J, Feng H, Tang Y. Primary multiple clear cell variant urothelial carcinomas of urinary bladder: A rare case report. Int J Clin Exp Pathol 2014;7(6):3385.

[13] Mai KT, Bateman J, Djordjevic B, Flood TA, Belanger EC. Clear cell urothelial carcinoma: A study of 10 cases and meta-analysis of the entity. Evidence of mesonephric differentiation. Int J Surg Pathol 2017;25(1):18-25. https://doi.org/10.1177/1066896916660195.

[14] Epstein JI, Netto GJ. Differential Diagnoses in Surgical Pathology: Genitourinary System. Philadelphia, PA: Lippincott Williams and Wilkins; 2014.

[15] Brimo F, Herawi M, Sharma R, Netto GJ, Epstein JI, Illei PB. Hepatocyte nuclear factor-1β expression in clear cell adenocarcinomas of the bladder and urethra: Diagnostic utility and implications for histogenesis. Hum Pathol 2011;42(11):1613-9. https://doi.org/10.1016/j.humpath.2011.01.007.

[16] Dadhania V, Czerniak B, Guo CC. Adenocarcinoma of the urinary bladder. Am J Clin Exp Urol 2015;3(2):51.