

Case Report

Clear cell urothelial carcinoma: a rare but villainous and hostile subtype

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Abstract: Clear Cell Urothelial Carcinoma (CCUC) is a rarely reported urothelial carcinoma variant first described in 1995. Due to CCUC's clinical rarity, reporting additional cases may aid future clinicians on surgical and oncological management. We present a case of an 89-year-old male with primary CCUC and highlight the aberrant histopathological findings with a literature review. This study aims to add to current descriptions of CCUC and inform surgical and oncological management in future patients. An 89-year-old male with a history of smoking presented to clinic with painless hematuria of six months duration. Imaging showed right-sided hydronephrosis down to a bladder mass. This was confirmed to be a bladder tumor on office cystourethroscopy. Following TURBT procedure, the pathology report came back suggesting 3.6 cm superficial low-grade Ta CCUC. Five months later, the patient presented with hematuria, acute kidney injury, and anemia. He was found to have T3a muscle-invasive urothelial carcinoma. This was confirmed on additional analysis which showed an FGFR3 mutation and abundant glycogen-filled clear cells. Histologically, CCUC is characterized by a glycogen-rich clear cytoplasm, severe atypia and a "nested" growth pattern. CCUC may be differentiated from non-CCUC by as few as a 30% clear cell change morphology of all cells. CCUC must be differentiated from Renal Cell Carcinoma and Clear Cell Adenocarcinoma. Treatment for CCUC has varied by case, with some surgeons electing to treat with radical cystectomy while others opting for local resection. Our case helps combat the paucity of literature by further characterizing and contributing to the management of CCUC.

Keywords: Urothelial carcinoma, clear-cell variant

Introduction

Bladder cancer is the second most common cancer of the genitourinary system and the eighth most common cause of cancer mortality in the United States [1, 2]. Urothelial carcinoma and non-urothelial carcinoma are the two main categories of bladder cancer. 90% of bladder cancers are urothelial carcinoma (UC), while 10% of non-urothelial bladder cancers include squamous cell carcinoma and adenocarcinoma [2]. The clear cell variant is a rare subtype of urothelial carcinoma accounting for <0.1% of total urothelial carcinoma cases [3]. The variants of urothelial carcinoma typically present with painless hematuria, voiding difficulties, and decreased urinary stream secondary to urethral obstruction, and are associated with similar epidemiological risk factors [4]. The

2024 American Urological Association guidelines for urothelial carcinoma variants include offering a Transurethral Resection of Bladder Tumor (TURBT) or radical cystectomy [5]. Clear cell variants were first described in the 1990s and only recently added to the WHO classification system of urinary tumors. Due to the scarcity of CCUC reporting, no established guidelines exist for specific treatment; however, previous aggressive interventions such as radical cystectomy have been utilized in management. Thus, CCUC treatment should be individualized. We present a case of an 89-year-old male with CCUC and highlight the aberrant histopathological findings with a literature review.

Case presentation

An 89-year-old frail male with a vague history of smoking presented to the clinic with painless

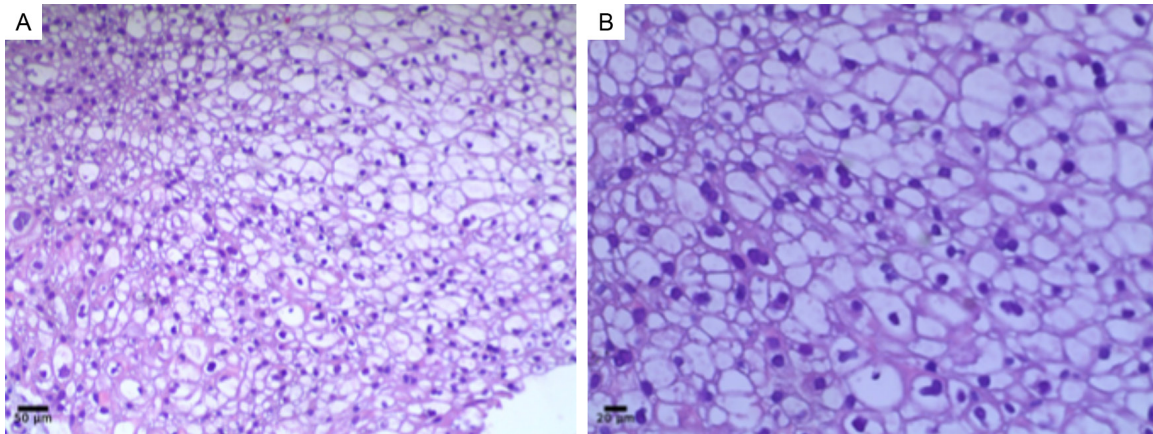


Figure 1. H&E staining of clear cell urothelial carcinoma. A. 200× magnified view of tissue shows clear cells with papillary pattern/architecture with scale bar set to 50 μm . B. 400× view shows glycogen rich clear cells in papillary formations with scale bar set to 20 μm Microscope manufactured by Nikon, Tokyo, Japan. Images calibrated with ImageJ.

hematuria of six months duration. His past medical history included atrial fibrillation, heart failure, and tinnitus. His medications were notable for warfarin. Computer Tomography (CT) of the abdomen/pelvis without contrast and renal ultrasound in combination demonstrated right-sided hydronephrosis down to a bladder mass. This was confirmed to be a bladder tumor on office cystourethroscopy. The patient subsequently elected for TURBT for removal.

Treatment

At the time of the TURBT, the affected collecting system could not be drained in a retrograde fashion. Interventional radiology (IR) was consulted postoperatively and the affected side was drained in an antegrade fashion. The stent was eventually internalized by IR. The pathology came back 3.6 cm superficial CCUC (**Figure 1**). The muscularis propria was present and not involved.

This was odd, since a bladder tumor in conjunction with new unilateral hydronephrosis is a sinister sign indicating advanced disease [6, 7]. The clinical and pathological findings thus were incongruent.

Due to the unusual pathology, we consulted a regional expert. The consultant, a Memorial Sloan Kettering trained experienced urological oncologist, reviewed the slides with our local pathologist, who sent them to joint pathology

conference for confirmation. The consultant only entertained local resection because of the frailty of the patient and his advanced age. The TURBT was repeated six weeks later and the pathology was low-grade Ta TCC of the bladder. The stent was removed in the office afterwards. Although this pathology, reverting back to a classic urothelial carcinoma confounded the surgical team, the patient's poor clinical status dictated conservative surgical management.

Follow up

Approximately five months after the original tumor resection, the patient was admitted for continuous bladder irrigation (CBI) due to urinary clot retention. The patient had acute kidney injury, progressive hematuria, and anemia as well as bilateral hydronephrosis down to a midline bladder tumor on CT. Subsequent Positive emission tomography (PET) scan suggested involvement of N1 nodes adjacent to the bladder and external iliac vessels, as well as in the left lateral lower lung field, mediastinum, and hilar regions (**Figure 2**). Despite the placement of catheter in for CBI, the bilateral hydronephrosis persisted and indicated a villainous recurrence. Repeat resection revealed a high-grade muscle-invasive urothelial carcinoma with clear cell features. The aggressive recurrent bladder tumor was the ultimate culprit of the gross hematuria, acute kidney injury from postrenal failure, and anemia from both acute blood loss and

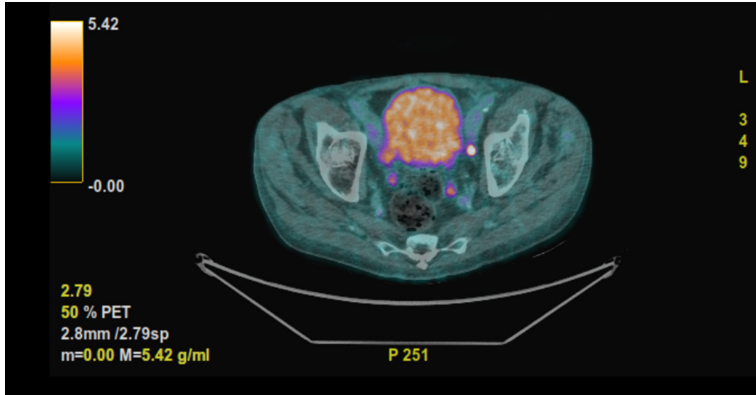


Figure 2. CT-PET imaging shows avid uptake in the internal iliac lymph nodes demonstrating metastatic disease.

anemia of chronic disease due to local metastatic disease. The biobehavior of this recurrence was consistent with prior reports describing CCUC as an aggressive subtype. Final staging conferred stage III-A disease with T2N1M0. Multidisciplinary tumor board discussion deemed patient a noncandidate for radical surgery based on stage III-A disease, frail status, and comorbidities. Therefore, the patient was referred to medical and radiation oncology.

Pathology staging showed T3a grade with a Fibroblast growth factor receptor 3 (FGFR3) alteration. Because of the patient's status and metastatic disease, he was started on concurrent chemoradiotherapy utilizing biweekly low-dose gemcitabine chemotherapy by the oncology consultant. The FGFR3 alteration suggested that this was a primary bladder tumor and not metastatic clear cell kidney cancer. This, along with clear cell histology, led pathology to making a final diagnosis of CCUC.

Discussion

Clear Cell Urothelial Carcinoma of the bladder is a rare malignant tumor first described in 1995 by Kotilar, Wood, Schaeffer, and Oyasu [8]. Clear cell variants of urothelial tumors may originate in the ovary, uterus, prostate, and kidney [9]. Prior CCUC cases provoked aggressive treatment, such as radical cystectomy, after diagnosis [9], yet to our understanding, concrete guidelines remain unavailable for best practices concerning CCUC due to its rare nature. Therefore, case reports are imperative for describing CCUC and its management.

Existing literature describes CCUC's histopathological appearance. Histologically, CCUC is characterized by a glycogen-rich clear cytoplasm [10]. Severe atypia and a "nested" growth pattern may also be observed [11]. CCUC may be differentiated from non-CCUC by as few as a 30% clear cell change morphology of all cells [9, 12]. Immunohistochemistry is helpful in final diagnosis due to the common occurrence of tumors containing clear cell morphology in the genitourinary system

[9]. The literature suggests that immunostaining in CCUC is positive for Cytokeratin 7 and CA-125, variable for Cytokeratin 20 and Carcinoembryonic antigen (CEA) staining, and negative for Vimentin, Prostate Specific Antigen, and CD-10 staining [9, 13-16]. In contrast, metastatic Renal Cell Carcinoma (RCC) typically stains negatively for Cytokeratin 7 and Cytokeratin 20 and positively for Vimentin [17]. Mai, Bateman, Djordjevic, Flood and Belanger note that in their case series, CK5 and CD44 staining were generally positive [9]. Unfortunately, we were unable to utilize immunohistochemistry analysis in this case. Thus, the clear-cell histology and FGFR3, a tumor marker for bladder origin, were utilized in the final CCUC diagnosis [18]. FGFR3 mutations and fusions are known oncogenes in bladder cancer [19, 20].

The differential diagnosis for CCUC includes clear cell adenocarcinoma (CCA), nephrogenic adenoma, and metastatic renal clear cell carcinoma to the bladder. Typically, CCA tissue may appear as tubulocystic, papillary, or diffuse on hematoxylin and eosin (H&E) stain [17]. Despite presenting similarly to CCUC; however, hobnail cells are often visualized in CCA and aid in its diagnosis [12]. Additionally, the absence of "chicken-wire" vasculature in CCUC may favor its diagnosis over CCA [9]. Signet ring cells must be excluded in the differentiation of CCUC and renal and prostatic adenocarcinoma [21]. These tumors generally exhibit mucinous granular cells with peripheral nuclei [21]. Thus, H&E staining with immunohistochemical analysis is critical in ensuring correct diagnosis. Additional differential diagnoses for

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CCUC include clear cell sarcoma and metastasis from the prostate, kidney, or ovary [17].

Management of CCUC has varied by case. Due to CCUC's ability to metastasize quickly, radical cystectomy has been performed on high-grade invasive tumors [9, 12]. In this case, however, the patient was at advanced age with significant comorbidities. Additionally, the original tumor was superficial and did not show invasion into the muscularis propria. Therefore, local resection using TURBT was utilized instead of radical cystectomy. This patient received a tailored regimen of biweekly gemcitabine along with radiotherapy. This treatment plan confirmed our surgical strategy in avoiding radical surgery in this frail patient at the extremes of age. Indeed, this surgical management differed from previous cases of CCUC, of which approximately 70% have been treated with radical cystectomy [12]. In summary, the patient's frail state and advanced age was a key determinant in both surgical and oncological treatment.

Prior literature suggests that an FGFR3 alteration can influence bladder cancer management. Patients with FGFR3 alterations may benefit from targeted therapy, such as with erdafitinib [22, 23]. Objective Response Rates (ORR) have been reported to be around 40%, which includes both partial and complete responses as seen in the BLC2001 study [22-24]. The presence of an FGFR3 alteration may confer low response rates in patients treated with platinum chemotherapy [25, 26]. Additionally, the tumor microenvironment in FGFR3 altered bladder cancers may alter the impact of immune checkpoint inhibitor therapies [27, 28].

The prognosis of CCUC is still being evaluated the majority of reported CCUC cases are aggressive, with an overall one-year survival of 52.9% [29]; however, there are reports of CCUC patients alive without recurrence [9, 17, 30, 31]. The patient remains alive one month after initiating biweekly gemcitabine and had muscle-invasive tumor recurrence after five months of initial TURBT. Due to the sparsity of literature, more reports are needed to fully understand CCUC prognosis.

Conclusion

CCUC remains a rarely encountered variant of urothelial carcinoma in the bladder. To our

knowledge, this is the 26th reported case of CCUC in the literature [9-13, 15-18, 21, 29-37]. This case of CCUC initially presented as superficial clear cell urothelial carcinoma; however, five months later, the patient had locally advanced metastatic disease muscle invasive disease. Compared to prior reported CCUC cases, this case confirms its reputation as a sinister actor. Our case is a cautionary tale with a superficial tumor advancing quickly in less than six months to metastatic disease. Although not appropriate in our frail patient, radical surgery should be considered in the right patient profile.

Disclosure of conflict of interest

None.

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