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Case Report **Internal Medicine**

Rare Clear Cell Variant Bladder Carcinoma Case

Qamar Adel Fallatah[1]*, Ahmad Taha Alkhiary[2], Badr M. Al-Joaid[3], Mohammed Salhab[4]

[1]Internal Medicine Resident, King Faisal Specialist Hospital & Research Center (KFSHRC)
[2]Histopathology Resident, King Faisal Specialist Hospital & Research Center (KFSHRC)
[3]Acting Chairman, Radiology Department; Consultant Abdominal Radiologist & Section Head, Abdominal Radiology, King Faisal Specialist Hospital & Research Center – Madinah
[4]Consultant, Medical Oncology, Department of Medicine, King Faisal Specialist Hospital & Research Center (KFSHRC)

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***Corresponding author:** Qamar Adel Fallatah
Internal Medicine Resident, King Faisal Specialist Hospital & Research Center (KFSHRC)

Abstract

Clear cell variants of bladder transitional cell carcinoma (TCC) are extremely uncommon. Identification, accurate diagnosis and deciding appropriate therapy for such variants are of clinical significance as they have aggressive clinical course and poor prognosis. A 54 years old male patient presented to emergency room (ER) on March, 2023 with history of gross painless hematuria and urine frequency for the past two weeks. Pre and postcontrast CT scan images from the patient's initial assessment were performed and showed mass-like wall thickening of the urinary bladder wall at the trigone. Cystoscopy revealed a bulging bladder lesion on the trigone of the bladder, followed by complete transurethral resection of bladder Tumor (TURBT) accordingly, complete resection was done. Histopathologically, the morphology and submitted immunostain slides showed strong positivity for CK7 and P63 which favor the diagnosis of urothelial carcinoma, clear cell subtype, the carcinoma extensively invades lamina propria and the carcinoma extensively invades muscularis propria.

Keywords: Clear Cell Variant, Transitional Cell Carcinoma, Bladder Carcinoma, Rare Variant, Transurethral Resection of Bladder Tumor, Urothelial Carcinoma.

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INTRODUCTION

Bladder cancer is relatively rare in Saudi Arabia with an incidence rate 1.4 per 100 000 individuals [1]. Transitional cell carcinoma (TCC) was the commonest histological type representing 95.7% of cases [2].

On global level, among variants of TCC of the bladder, clear cell variants are extremely uncommon [3]. Identification, accurate diagnosis and deciding appropriate therapy for such uncommon variants is of clinical significance as they have aggressive clinical course and poor prognosis [4].

We present an extremely rare case of clear cell variant of bladder carcinoma, that characterized by an extremely fast tumor growth.

CASE REPORT

This is a 54 years old male patient presented to emergency room (ER) on March, 2023 with history of gross painless hematuria and urine frequency for the past two weeks. Personal history revealed that he was heavy smoker (more than 2 packs per day for 20 years) with no past medical history. The patient was evaluated after two days in outpatient department (OPD), his vitals within normal range, body mass index was 21.8 kg/m^2. Lung auscultation showed normal breath sounds were equal and cardiac examination showed S1, S2 with no murmur, abdomen was soft and lax.

Pre and postcontrast CT scan images from the patient's initial assessment showed a mass-like wall thickening of the urinary bladder wall at the trigone which was smaller in size, encroaching on bilateral ureterovesical junction associated with bilateral mild hydroureter and hydronephrosis, more to the left side (measuring 22 × 9 mm compared to 18 × 6 mm on previous exam. No lymphadenopathy in abdomen and pelvis, stable too small to be characterized liver lesions in segment #5 and segment #4A likely representing small cysts or haemangiomas, no new liver lesions and no evidence of metastatic disease in abdomen and pelvis. Figure 1.

Cystoscopy and Transurethral Resection of Bladder Tumor (TURBT) were done on 13 April, 2023 and showed bladder lesion on the trigone of the bladder (bulging lesion not papillary), accordingly, complete resection of all visible tumor was done. Histopathology showed adenocarcinoma with variant like clear cell urothelial cancer and invasion to the muscularis propria (muscle invasive). Immunostain slides showed strong positivity for CK7 and P63 which favor the diagnosis of urothelial carcinoma. However, the focal positivity for CK20, GATA-3 and PAX8 may suggest clear cell adenocarcinoma. Although the tumor cells are negative for RCC markers. Prostatic surface antigen (PSA) was negative. Ancillary studies reported scattered large atypical cells with round nuclei, single prominent nucleoli, and vacuolated abundant clear cytoplasm are noted in a background of degeneration, blood, and debris.

The differential diagnosis included clear cell adenocarcinoma, clear cell variant urothelial carcinoma and metastatic clear cell carcinoma. Staging CT did not reveal any signs of advanced or metastatic disease, and disease considered localized, but patient deemed not a candidate for neoadjuvant chemotherapy due to clear cell variant histology. Patient was extensively counseled for radical cystoprostatectomy with pelvic lymph node dissection and urinary diversion (orthotopic neobladder versus ileal conduit) with explicit recommendation against bladder preservation, as clear cell variant lacks evidence for organ-preserving protocols but the patient declines and lost follow-up and presented after 1 year with metastatic disease to bone.

Patient was treated with palliative systemic Enfortumab vedotin (EV) + pembrolizumab similar to the current of care for bladder cancer and avoided platinum based chemotherapy for such clear cell variant which would not typically response to platinum based chemotherapy, received 7 cycles with good partial response on restaging imaging then followed with palliative radiotherapy to bladder and pelvic bone metastatic due to pain.

In conclusion, muscle-invasive high-grade urothelial carcinoma of the urinary bladder, clear cell subtype was diagnosed, with extensive invasion of muscularis propria on trigone. Patient treated with immunotherapy combination treatments upfront rather than platinum and had a good response in extrapolating from the sensitivity for clear cell histology for immunotherapy based treatments.

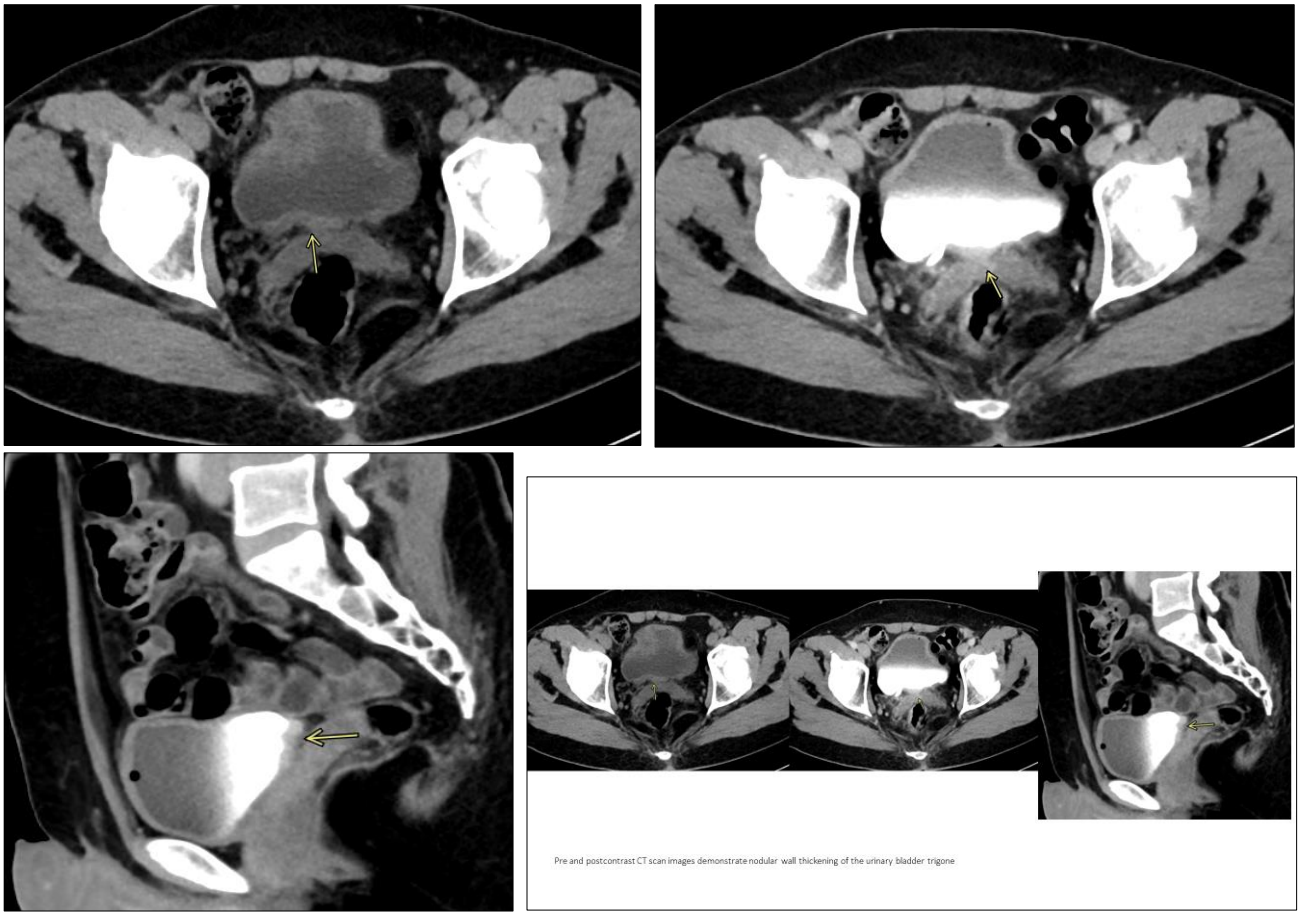
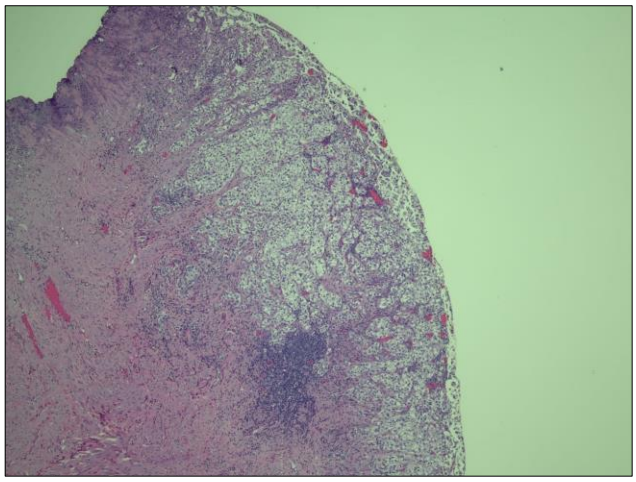
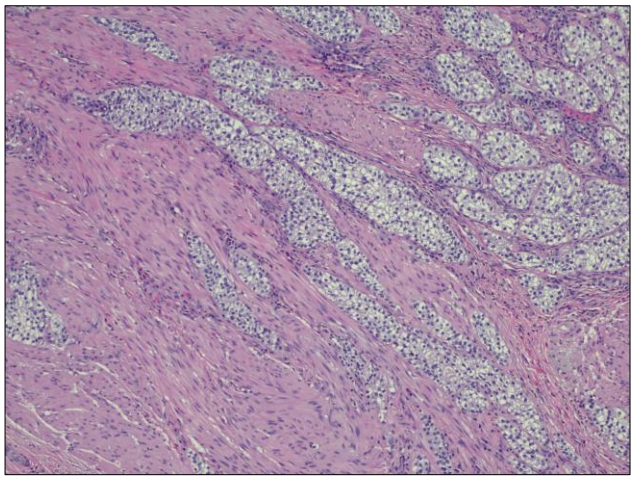


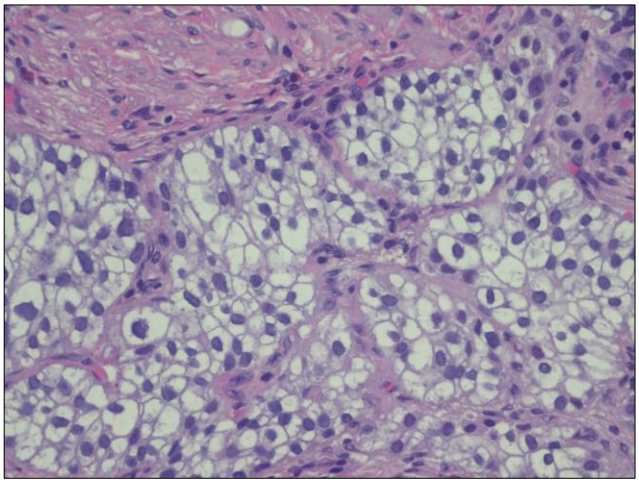
Figure 1: Pre and postcontrast CT scan images from the patient's initial assessment demonstrate nodular wall thickening of the urinary bladder trigone



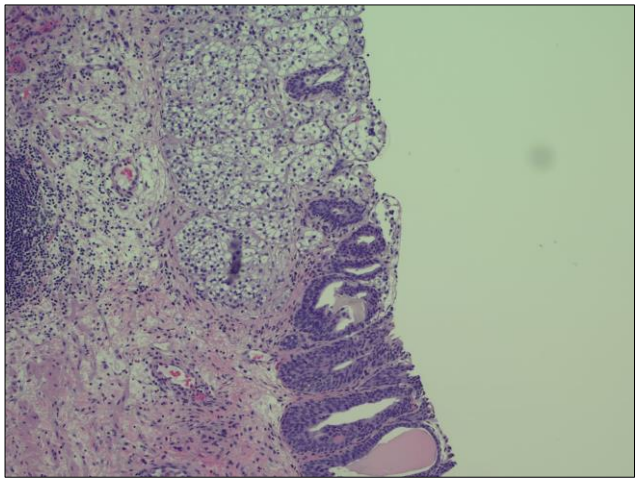
1. Low power view (4x)



2. Cancer infiltrating the muscularis propria (20x)



3. High power view of the cancer cells (40x)



4. Bonus picture showing the transition from the classic urothelial appearance to the clear cell variant (10x)

Figure 2: Histopathological imaging studies for the case demonstrating a clear cell variant

DISCUSSION

Bladder carcinoma has different histopathological variants, some of these variants have aggressive course [5]. Of which, clear cell variant of TCC which is a rare type described by Kotliar *et al*., in 1995 [6], and added to the classification of the urinary system's tumors in 2016 [5].

Nearly about 20 cases were reported since that time. A cut-off percentage of approximately 90% of clear cells was used to definitely diagnose clear cell urothelial carcinoma [7]. However, Mai *et al.,* (2017) suggested that clear cell variant can be differentiated from non-clear cell variant of TCC of the bladder by the extensive clear cell change in over 30% of cells [8].

This variant commonly affects males with an age range of 55-82 years [9], which coincides with our case (male aged 54 years). Furthermore, cases are commonly presenting with gross hematuria and less commonly increased frequency, dysuria, anuria and urgency [9]. The present case presented with painless hematuria and increased frequency.

Despite the fact that clear-cells can be visualized through microscopic evaluation of urothelial carcinomas' variants, clear cell variant consists of mainly or exclusively of clear-cells [10].

Urinary bladder clear-cell adenocarcinoma, lipoid cell variant, prostatic adenocarcinoma and metastatic clear-cell renal cell carcinoma were included in the differential diagnosis. However, Urinary bladder clear-cell adenocarcinoma predominantly affects female urethra despite some reported cases affects male urinary bladder [6]. Lipoid cell variant is characterized by existence of multivacuolated lipid droplets [11]. Prostatic adenocarcinoma might show clear cells; however, it was excluded by negative PAS test.

In the present case, PAX-8 was positive and other tumors were excluded by clinical presentation, morphology, and a panel of immunohistochemical stains. Positivity for GATA3 confirmed the urothelial origin of the tumor.

It has been documented in previous reports that clear cell variant of TCC of the bladder was associated with aggressive clinical courses [12-14], with 1-year survival rate of 52.9% and majority of cases (82.6%) showed muscle invasion as well as a considerable proportion of cases (16.7%) presented with metastasis to lungs and bones at the time of diagnosis. In addition, some case developed rapid progression after radical cystectomy [14].

Multidisciplinary assessment for consideration of neoadjuvant/adjuvant chemotherapy, in addition to radical cystectomy and lymphadenectomy has been recommended for patient with muscle-invasive clear cell variant TCC of the bladder for better tumor response and survival [15], in accordance with American Urological Association (AUA) and Canadian Urological Association (CUA) guidelines [16, 17]. In the present case, multidisciplinary tumor board systemic treatment along the lines of clear cell/non-conventional histology were adopted.

Conclusively, clear-cell variant TCC of the bladder is a very rare histopathologic type with mostly aggressive clinical course. Its differential diagnosis can be confirmed by conventional histology and immunohistochemistry. Thus, it is of vital importance to the pathologist to make a clear decision based on microscopic findings for initiating appropriate management.

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