# More Than Meets the Eye: a Case of Synchronous Ipsilateral Clear Cell Renal Cell Carcinoma and Urothelial Carcinoma of the Pelvicalyceal System

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**Case Report**

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# Abstract

**Background:** The synchronous occurrence of renal cell carcinoma and urothelial carcinoma of the renal pelvis in the same kidney is extremely rare, although previously reported. To our knowledge, we present the youngest patient recorded in the literature, with this histology combination presenting synchronously in the same kidney, and the first report in active duty military personnel.

**Case presentation:** An otherwise healthy 43-year-old military male with the chief complaint of left plank pain was seen in the office. Imaging revealed the presence of a 3.5 cm left renal mass. Left laparoscopic radical nephrectomy was performed for presumed renal malignancy. Pathology confirmed the presence of a clear cell RCC and revealed an area of low-grade UC arising from the ipsilateral renal pelvis, not visible in the preoperative imaging.

**Conclusions:** Although uncommon, the final pathology report may reveal neoplasms of dissimilar histology that may involve the renal pelvis. It is crucial for urologists and pathologists to be vigilant of such cases during a solid renal mass workup. Additional therapeutic adjustments may be necessitated, derailing the initial treatment plan. Novel biomarkers of cancer stem-like cells may play a role in the management of these patients.


# Background

Since the first reported case by Graves et al. in 1921 [1], synchronous renal cell carcinoma (RCC) and urothelial carcinoma (UC) in the same kidney remain infrequent, with approximately 40 cases to date [2].

We present a case of an incidentally discovered UC of the renal pelvis in the pathology specimen of a laparoscopic radical nephrectomy performed for a presumed renal malignancy in the same kidney. To our knowledge, this is the youngest patient with this type of histology combination, presenting concurrently in the same kidney, reported in English literature and the first report in active military personnel.

# Case Presentation

A 43-year-old active-duty male was seen in the office with dull, left plank pain of five days' duration. The patient also complained of generalized fatigue for the past month, which he attributed to increased workload. He denied any trauma, gross hematuria or pain during urination in the days leading up to the presentation. Past medical and surgical history was unremarkable. A 10-pack-year history of cigarette smoking, but no occupational chemical exposure was reported. Genitourinary or associated genetic disorders were also absent in any family member.

On initial assessment, the patient had a BMI of 28 $kg/m^2$, a temperature of $36.5^0$C, blood pressure 120/80 *mm Hg*, pulse 75*/min*, and respiration rate 16*/min*. No costovertebral angle tenderness or palpable masses were felt.

Routine blood work showed a marginally elevated aspartate transaminase (AST) and alanine transaminase (ALT), 35.6 *IU/L* (normal 5.0–34.0 g/dL) and 58.6 *IU/L* (normal 7.0–55.0 *g/dL*) respectively, LDH of 346.3 (normal 125.0-220.0 *IU/L*), creatinine in the upper limit of normal 1.19 *mg/dL* (normal 0.72–1.25 *g/dL*); full blood count, electrolytes, and coagulation studies were within normal limits. Urinalysis showed 8 red blood cells/*hpf (high power field).* Urine culture and a Meares-Stamey test came back negative for abnormal findings.

The patient was subsequently sent for computed tomography (CT), which revealed a 3.5 cm mass in the anterior aspect of the left mid-pole with heterogenous enhancement and a normal-appearing contralateral kidney. The lesion was noted to slightly compress and displace without invading the left renal pelvis and renal vein. No involvement of the retroperitoneal lymph nodes and adrenals was seen *(*Fig. 1*)*. Additionally, the baseline chest CT scan was normal. At this time, our impression was possible renal cell carcinoma, necessitating mass removal and histological examination. Left laparoscopic radical nephrectomy (LRN) using the transperitoneal approach was performed. The patient did well postoperatively and was discharged in 3 days.

The left kidney weighing 320 *gr.*, perinephric adipose tissue, and a 3.5 x 0.5 cm segment of the left ureter were resected. On cut section, a 3 cm well-circumscribed, centrally located mass, in close proximity to the renal hilum, was detected. The mass had a brown and orange-colored variegated cut surface. The perirenal fat tissue could be easily detached from the renal capsule, and no involvement of the Gerota's fascia was appreciated. In addition, two whitish nodules of 0.4 to 0.6 cm were found in the periphery. On light microscopy, the first tumor was a Fuhrman nuclear grade 3 clear cell RCC *(*Fig. 2*)*. No capsular penetration and invasion of renal parenchyma and pelvis was noted. The grossly whitish nodules were interpreted as low-grade, papillary UC originating from the renal pelvis, pT1 *(*Fig. 3*)*. No parenchymal invasion was seen. Tumor cells on this part were negative for cluster of differentiation 10 (CD10) and positive for cytokeratin 7 (CK7) on immunohistochemistry *(Fig. 4)*. All surgical margins, including the ureteral margin, were free of tumor and no lymphovascular and neural invasion was seen.

In light of the UC and following extensive discussion, the patient elected to undergo further surgical treatment. Cystoscopy followed by open left ureterectomy with bladder cuff excision was performed three weeks after the first operation. Cystoscopy, urinary cytology, and distal ureter stump pathology showed no evidence of disease. The patient was discharged to be followed by a modified surveillance protocol of cystoscopy, urine cytology, and CT for the next five years.

# Discussion

RCC and TCC represent the majority of renal malignancies in adults comprising together 90–95% [3]. The coexistence, however, of the two most common histological subtypes of renal tumors in the same kidney is extremely rare, approximating 0.14% as per a previous study [4].

Concurrent RCC and TCC of the renal pelvis present with a mean age of 64.5 years, more commonly in the left side, such as in our case, and are twice as common in males, resembling the epidemiology of

independent RCC or TCC of the kidney, as demonstrated by Hart et al. in a review of 23 cases [5]. Strikingly enough, our patient was 43 years old, making him the youngest case on record to the best of our knowledge. Moreover, it represents the first report in active military personnel. Previously, Kline et al. had reported on a 47-year-old patient in an era when CT urography was practically nonexistent [6].

In the same retrospective study by Hart et al., cigarette smoking was implicated in 24% of the cases [5]. TCC of the renal pelvis may be associated with the abuse of phenacetin-based compounds. Anseline et al. in 1977 described this histological combination in a woman with analgesic nephropathy [7], in accordance with Bengtsson et al. initial findings in 1968 [8]. Our patient denied the use of analgesics and exposure to other known renal carcinogens apart from tobacco. Moreover, Park et al. proposed that c-MET and p53 may be associated with the development of papillary TCC of the renal pelvis, based on their immunohistochemistry findings [9].

Interestingly, we are witnessing a paradigm shift in the preoperative diagnosis of such cases. Traditionally, the renal pelvic tumor was diagnosed first, using retrograde pyelograms, during the workup of hematuria, and the RCC was an incidental pathology finding [4]. Nowadays, most renal tumors and more than 50% of RCCs are detected accidentally due to the US and CT's widespread use for other medical indications [10]. Consequently, similarly to our case, detection of an asymptomatic RCC usually precedes that of TCC.

Regarding management, surgical treatment of RCC and upper tract UC are fundamentally different. RCC is managed by radical or partial nephrectomy, with the latter suggested mainly for localized T1 RCC [10]. Upper tract UC management, on the other hand, relies on risk stratification to select those patients who will benefit more from a kidney-sparing treatment. Histological and cytological grades of cancer cells are crucial factors, although not the only ones, to consider for risk stratification. With that being said, kidney-sparing surgery (KSS) for low-risk disease and RNU with bladder cuff excision for high-risk disease are recommended [11].

Due to the unfavorable location of close proximity to the renal hilum, we decided to proceed with a laparoscopic RN, even though we had to deal with a T1 tumor.

In view of the incidental UC in the renal pelvis after RN, management of the remaining ureteric stump remained a therapeutic dilemma. Previous series have shown recurrence rates ranging from 20 to 58 % in the ureteral stump after incomplete nephroureterectomy for TCC of the upper tract and seem to increase proportionately to the length of the remaining ureter [12]. On top of that, a study from Mayo Clinic suggested that grade 2 tumors carry a 30 % rate of ipsilateral tumor recurrence, meriting a radical nephroureterectomy. Conversely, the less frequent ipsilateral recurrence in grade 1 tumors may allow a less radical approach [13].

In our case of a low-grade TCC of the renal pelvis found after RN, one could argue in favor of surveillance instead of a more extensive surgical treatment. An interesting case of active surveillance with cystoscopy, ureterograms, ureteral washings, and ureteroscopy of the ureteral stump is reported by Michel and

Belldegrun [14]. Of note, the patient must be aware of the stringent follow-up that active surveillance entails to make an educated choice. Our patient elected to complete the surgical treatment to avoid this strict surveillance and eliminate anxiety around a potential recurrence.

Cancer stem-like cell (CSC) markers, such as cluster of differentiation 44 (CD44) and aldehyde dehydrogenase 1 A1 (ALDH1A1), may give insights into the prognosis of urologic malignancies [2]. Lu et al. reported the first patient with recurrence of both RCC and UC, in the ipsilateral adrenal and bladder respectively, despite the use of adjunct chemotherapy and clear surgical margins. The high incidence of metastatic recurrences may be associated with the abnormal expression of CSC markers in primary or recurrent lesions, before and after chemotherapy, as demonstrated in Lu's case [2]. However, their role as markers of chemotherapy resistance or potential therapeutic targets remains to be seen.

# Conclusions

This case report highlights a synchronous occurrence of RCC and UC of the renal pelvis in a 43-year-old patient. The rarity of two simultaneous primary renal malignancies of dissimilar histology and the patient's age merits reporting. Oftentimes, physicians rest assured of a diagnosis once detection of a renal parenchymal tumor on imaging is being made. Meticulous pathologic examination and clinical suspicion are necessary to uncover the co-existence of a second malignancy providing the optimal treatment, even when that requires a change in the initial therapeutic plan. Novel biomarkers of cancer stem-like cells may play an important role in the prognosis and therapy of urologic malignancies.

# Abbreviations

RCC: Renal cell carcinoma; UC: Urothelial carcinoma, AST: Aspartate transaminase; ALT: Alanine transaminase, CT: Computed tomography, Hpf: High power field, LRN: Laparoscopic radical nephrectomy, KSS: kidney-sparing surgery, CD10: cluster of differentiation 10; CK7: cytokeratin 7; CSC: Cancer stem-like, CD44: cluster of differentiation 44; ALDH1A1: aldehyde dehydrogenase 1 A1

# Declarations


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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Authors' contributions

AS designed the study, performed the literature search, and drafted the manuscript. IT reviewed the radiologic images, described findings, prepared figures, edited, and drafted the manuscript. AM assisted in literature searching, edited the radiological images, and suggested manuscript edits. IT performed the histopathological image analysis, prepared figures, and edited the manuscript. IT, ENS, CG, CG, AM, MP contributed to the study conception, assisted in the initial drafting of the manuscript, revised, and edited the final manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy is available for review by the editor of this journal.

### Competing interests

The authors declare that they have no competing interests.

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## Figure

Figure 4 is not available with this version.

## Figures

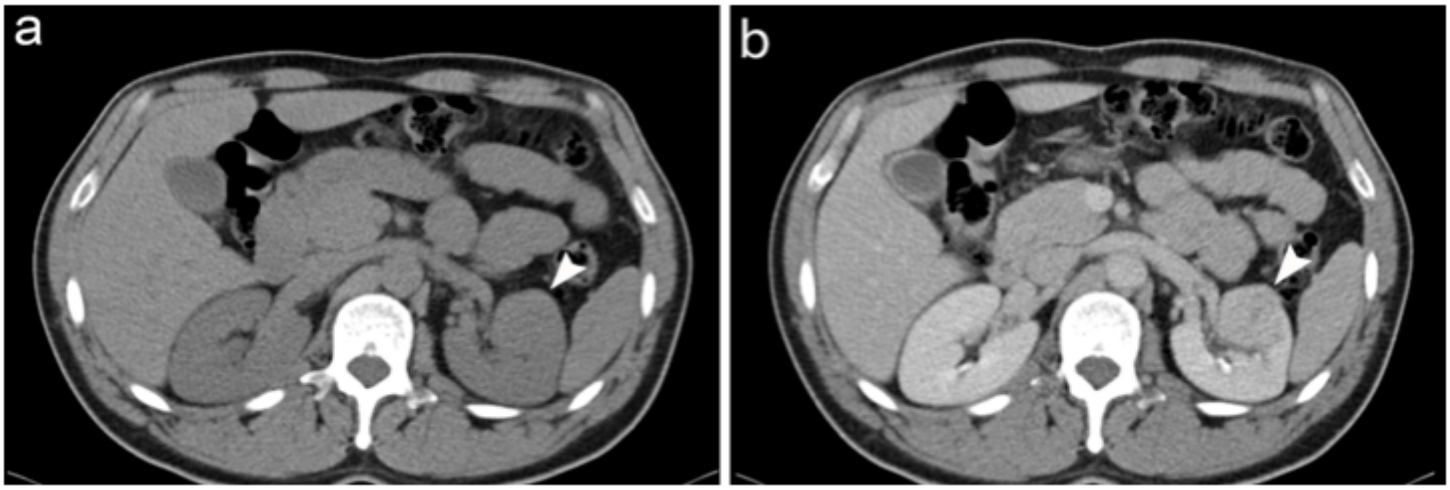


**Figure 1**

CT of the abdomen before (a) and after intravenous contrast administration (b) reveals the presence of a 3.5 cm mass in the anterior aspect of the mid-pole of the left kidney with heterogenous enhancement and a normal-appearing contralateral kidney. The lesion was noted to slightly compress and displace without invading the left renal pelvis and renal vein. No involvement of the retroperitoneal lymph nodes and adrenals was detected.

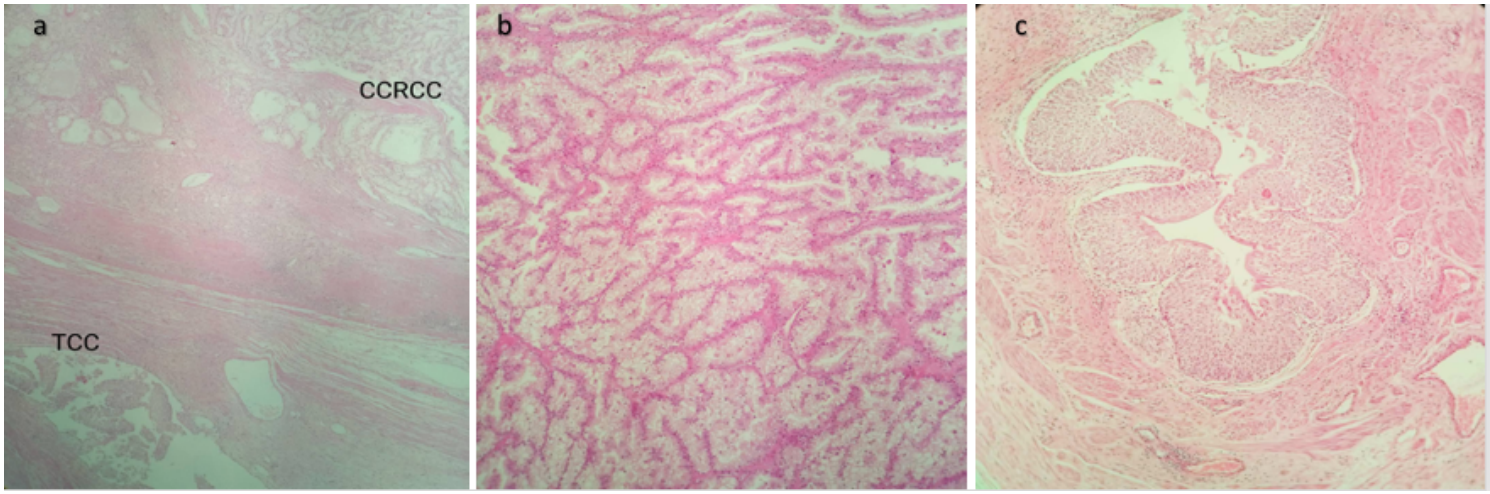


**Figure 2**

Section of the tumor at the middle part of the left kidney: (a) Renal cell carcinoma (upper right) and transitional cell carcinoma (lower left) captured together. (b) Clear cell renal cell carcinoma, Fuhrman's nuclear grade 3. (c) Low-grade, papillary urothelial carcinoma arising from the renal pelvis (Hematoxylin and eosin, original magnifications x40, x100 and x100, respectively)

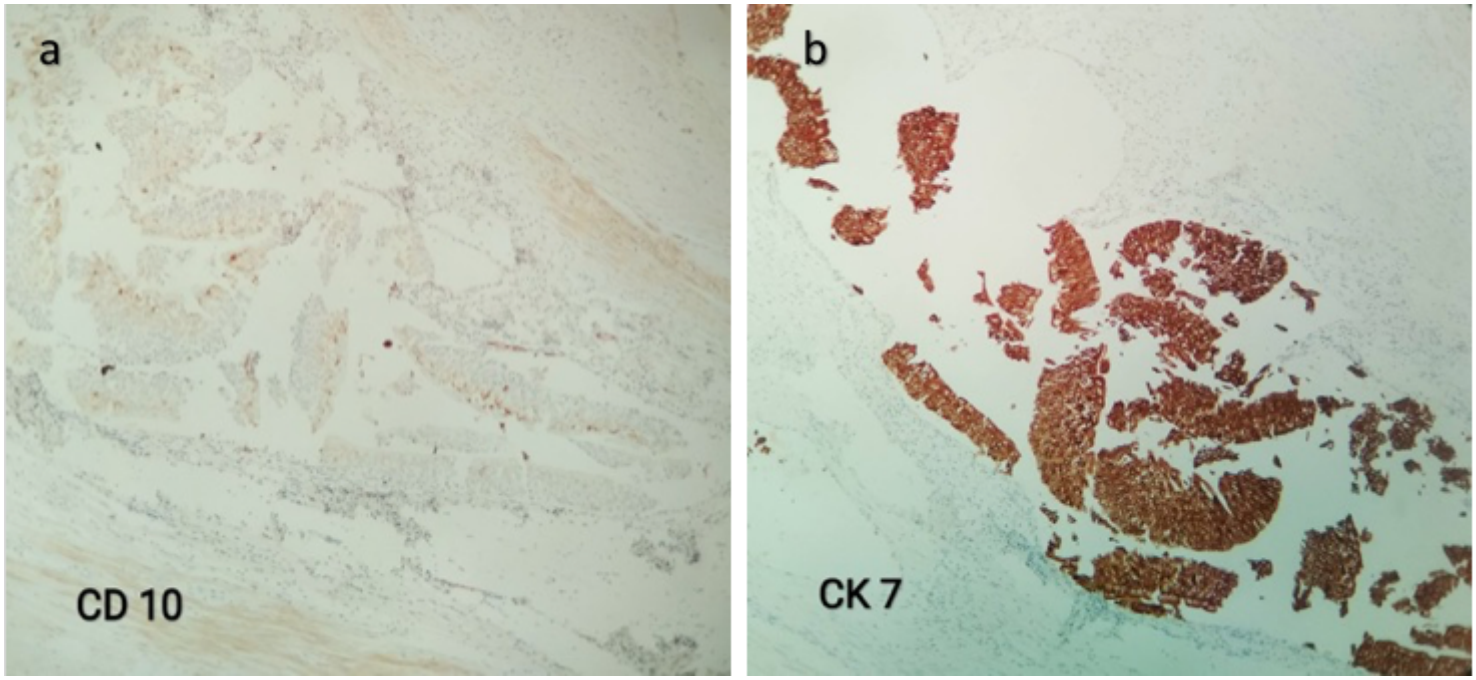


**Figure 3**

Transitional Cell Carcinoma of the renal pelvis (Original magnifications x100): (a) Cells stained negative for CD10 immunohistochemical stain. (b) Cells stained positive for CK7 immunohistochemical stain