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Novel Insights from Research Practice

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Multifocal Urinary Tract Metastasis of Colorectal Carcinoma

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Established Facts

- True ureteral and renal pelvis metastases are rarely present.
- The separation of metastatic colorectal carcinoma from primary adenocarcinoma of the urinary tract can pose diagnostic difficulties.

Novel Insights

- This is the first case reported with concurrent ureteral and renal pelvis metastases of colorectal adenocarcinoma.
- In our experience, DNA sequencing proved to be a safe diagnostic tool to differentiate between primary and metastatic adenocarcinoma of the urinary tract.

Keywords
Urinary tract · Metastasis · Differential diagnosis · Sequencing

Abstract
Introduction: Secondary urinary tract tumors are uncommon findings and mainly evolve by direct invasion from adjacent organs. Actual metastatic involvement often develops in the urinary bladder, while the upper urinary tract is infrequently affected. In addition, the lungs, breast, and prostate gland are the usual primary sites. Colorectal carcinoma (CRC) may spread to the ureter directly or seeds via vascular or lymphatic channels. It may pose struggles in the differential diagnosis because CRC shares standard pathologic features with the primary adenocarcinoma of the urinary tract. ***Case Presentation:*** We describe the case of an 81-year-old man who was referred to our hospital with a distal ureteral tumor

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that was treated by a ureteronephrectomy. The histopathological and genetic analysis established the diagnosis of metastatic CRC along with 3 metastases in the renal pelvis. ***Conclusion:*** This rare case highlights the limitations of conventional histological processing, including immunohistochemistry, and it underlines the role of molecular investigations in certain circumstances.

Introduction

The obstruction of the ureter by direct invasion of retroperitoneal or minor pelvic tumors is relatively frequent. In contrast, the development of a true ureteral metastasis from distant primary tumors (such as the lung, breast, and prostate gland) is an unusual event, with approximately 400 cases reported [1]. Accordingly, CRC may invade the distant section of the ureter directly or via lymphatic channels and blood vessels [2], but hematogenous metastasis to the renal pelvis is a scarce event with rare case reports in the English literature [3]. Nevertheless, no data were found regarding the phenomenon of the concurrent renal pelvis and ureteral metastases in disseminated CRC. Of note, metastatic involvement of the ureter is frequently associated with extensive tumor burden; hence, it is often diagnosed postmortem [4]. The diagnosis of metastatic CRC of the ureter is usually based on the clinical data and the exclusion of primary ureteral tumors. Immunohistochemically, there are no decisive markers; hence, the pathological diagnosis can be challenging [5]. Here, we report the coexistence of both ureteral and renal pelvis metastasis of a CRC.

Case Report

Here, an 81-year-old male patient with left-sided hydronephrosis was admitted to our institution. Two years ago, a sigmoid colon carcinoma was discovered and treated by a left hemicolectomy. The pathological analysis revealed an intestinal-type adenocarcinoma with pT3pN1a pathological stage. Moreover, extensive tumor budding along with lymphovascular invasion was observed. The molecular investigations carried out identified a *KRAS* mutation in codon 12 (G12D). The patient received adjuvant chemotherapy with 6 cycles of capecitabine, which was tolerated well, and no significant side effects were recorded. The follow-up from May 2019 to September 2020 was uneventful. Then, the patient complained of hematuria, and, at first, a cystoscopy was carried out that described no bladder tumor, inflammation, or stone but noticed blood leakage from the left ureteral orifice. Additionally, a rigid ureteroscopy was unsuccessful; therefore, any histological sampling or upper urinary tract washing for cytology was impossible. The next step was a contrast-enhanced abdominal CT, which showed a distal ureteral mass causing severe, grade IV, left-sided hydronephrosis with thinned, impaired renal parenchyma (Fig. 1a). At the multidisciplinary team meeting, the lesion was considered a primary ureteral urothelial cell carcinoma (UCC). As no additional information was expected from another imaging technique, a presumably curative surgery was decided. Consequently, a left-sided ureteronephrectomy and lymph node dissection were carried out. The surgery and the postoperative period were uneventful. After a 2-month-long recovery, as part of restaging examinations, a whole-body FDG PET/CT was performed that described lytic metastasis in the body of vertebra VII, seventh rib on the left side, and parietal bones, but it did not prove other distant metastasis or local recurrence. Palliative radiotherapy with a 10 × 3 Gy total dose was planned, but due to the severe acute respiratory distress syndrome caused by COVID-19 infection, the patient deceased just 67 days after the surgery.

Pathological Findings

The gross analysis of the ureteronephrectomy specimen revealed a 60-mm large tumor in the distal part of the ureter along with 3 masses in the renal pelvis (Fig. 1b). Also, severe dilation of the urinary tract was observed, and there was a macroscopically evident resection line positivity. The histological investigation identified these lesions as intestinal-type adenocarcinomas with the typical cribriform pattern and dirty necrosis in their lumina. The ureteral tumor affected all layers and destroyed most of the surface urothelium (Fig. 1c, d). Two tumors had an exophytic growing pattern in the pelvis, while 1 lesion infiltrated the renal parenchyma and renal sinus (Fig. 2a–c). Here, the urothelium showed no sign of dysplasia; besides, no glandular metaplasia was observed (Fig. 2d). The tumor cells were present in the circumferential resection line; furthermore, in the lymph nodes harvested, the metastasis of the same adenocarcinoma was seen. We applied immunohistochemical studies to clarify the origin of the tumors. The results were as follows: all tumors and the lymphatic metastasis were positive with CK20 and CDX2 in a diffuse fashion (Fig. 2e, f); besides, the CK7 and GATA3 staining was negative. Interestingly, we experienced a diffuse and membranous beta-catenin expression in the samples examined (Fig. 2g), and we observed this membranous pattern in the previous colonic adenocarcinoma. At this point, the exact origin of the neoplasms was still uncertain since both the light microscopy and the immunohistochemical analysis were inconclusive. A *KRAS* sequencing was ordered from the tumors in the renal pelvis, ureter, and lymph node. The molecular pathological examination identified a pathological mutation in codon 12 (G12D) in all tumors (Fig. 2h). A microsatellite instability analysis was additionally requested that revealed a stable microsatellite status. After a 2-month-long recovery, a whole-body FDG PET/CT has been scheduled that described lytic metastasis in the body of vertebra VII, seventh rib on the left side, and parietal bones. Palliative radiotherapy with a 10 × 3 Gy total dose was planned, but due to the severe acute respiratory distress syndrome caused by COVID-19 infection, the patient deceased just 67 days after the surgery.

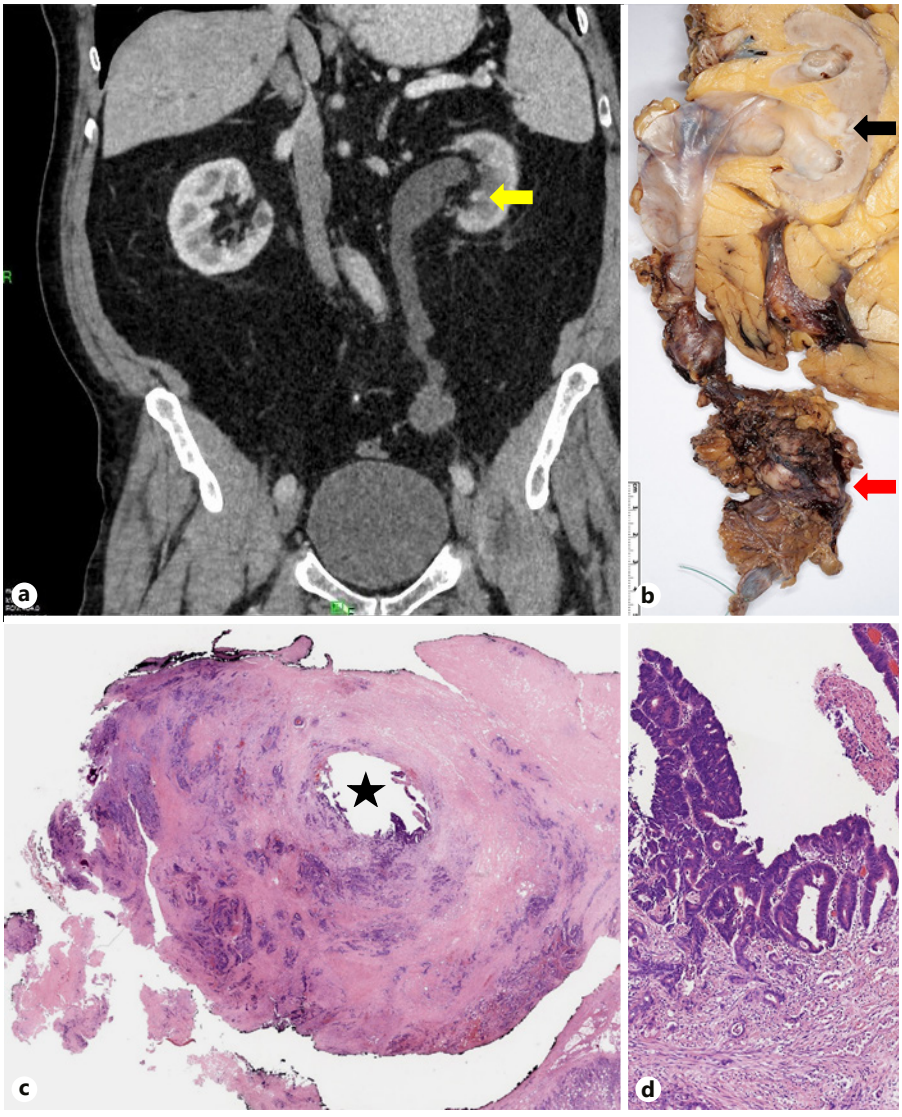

Fig. 1. Radiological and pathological features of the case presented. **a** Axial enhanced abdominal CT scan (soft tissue window) shows an inhomogeneous, contrast-enhanced, lobulated lesion (30 × 41 × 32 mm) in the low third segment of the left ureter, causing an obstruction and severe hydronephrosis. In this case, the hydronephrosis is grade 4. The dilatation of the renal pelvis and calyces with cortical thinning indicates an irreversible renal functional loss. The renal pelvis metastasis (yellow arrow) accumulates the intravenous contrast agent better than the damaged renal parenchyma in the venous phase. **b** The corresponding macroscopic picture demonstrates the hydroureter along with hydronephrosis. The black arrow points at a lesion that originates from the renal pelvis, but signs of parenchymal invasion are present. Additionally, the red arrow indicates the tumor obstructing the lower third part of the ureter. **c** In the cross-section of the ureter, an invasive carcinoma with transmural and mucosal infiltration can be seen. The asterisk illustrates the lumen of the ureter. The image has a magnification factor of ×7. **d** Most of the inner surface of the ureter was ulcerated; however, in some areas, atypical glandular proliferation was found. The image has a magnification factor of ×10.

Discussion

Here, a patient with an assumed UCC of the distal ureter underwent ureteronephrectomy, and the histological analysis uncovered coexisting ureteral and renal pelvis metastases originating from the previous colon adenocarcinoma. Here, we discuss the possible mechanisms of the observed phenomenon and diagnostic pitfalls.

Metastatic tumors can invade the ureter by direct extension and via vascular or lymphatic channels [2]. Regarding the former mechanism, cervical cancer is the most frequent reason, followed by CRC and other retroperitoneal tumors like lymphoma, liposarcoma, etc. [6]. On the other hand, a true distant metastasis to the ureter is an unusual phenomenon. The primary tumor is mostly discovered in the lungs, breast, prostate gland, and sometimes in the colon [7]. Clinically, unilateral or bilateral hydronephrosis is the usual complication experienced in these cases, and the obstruction usually results from an outside compression rather than a real invasion [8]. In addition, hematuria is seldom noticed because the urothelium mostly remains intact [8]. Interestingly, in cases of true metastatic involvement, the lower third part of the ureter is typically affected. In our case, we experienced a slightly different clinical scenario because the ureteral metastasis showed transmural involvement. Uniquely, the urothelium itself was destroyed or focally replaced by the tumor cells; therefore, similar

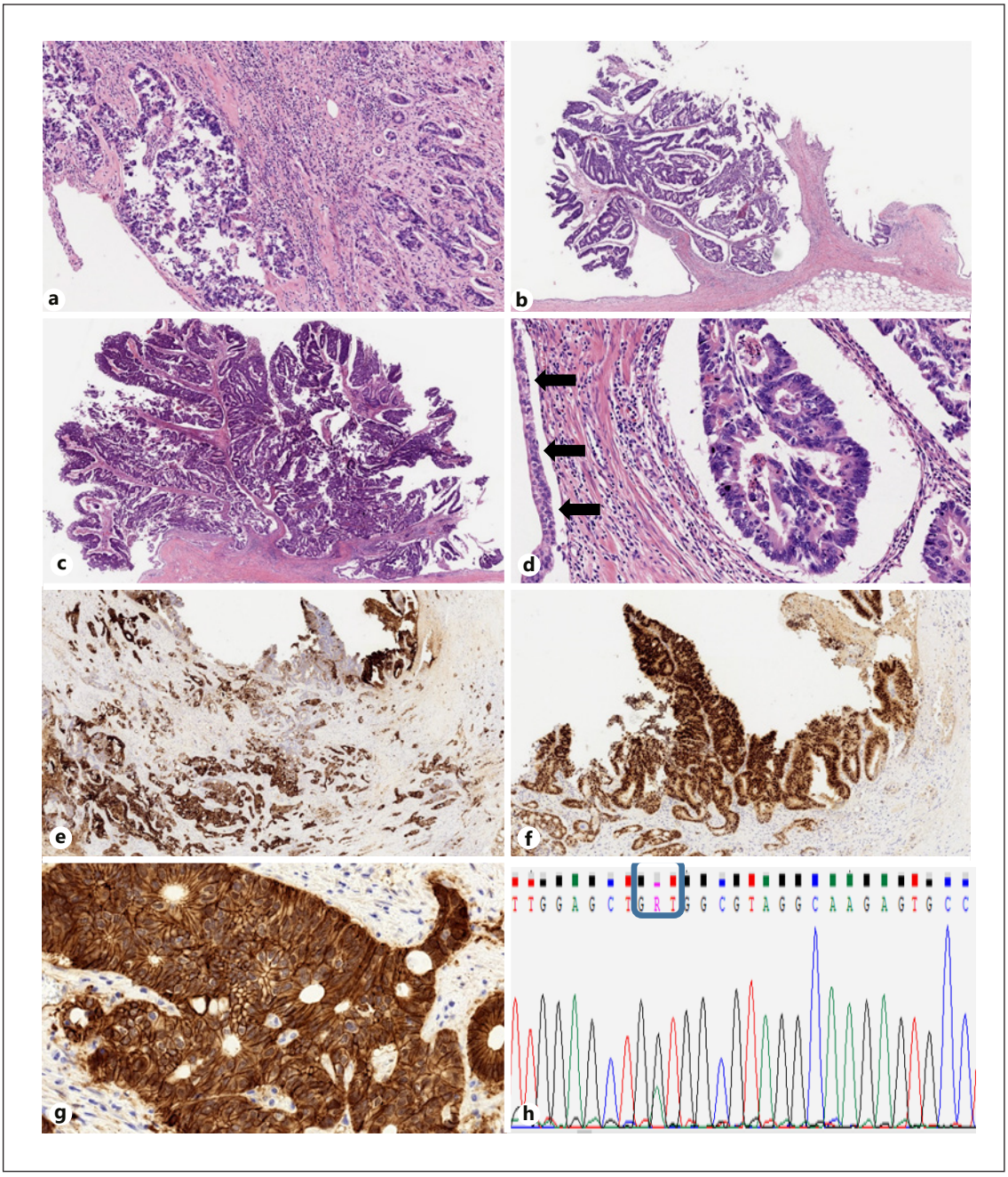

Fig. 2. Histological, immunohistochemical, and genetic features observed. **a** This renal pelvis metastasis has a flat appearance along with the invasion of the adjacent renal parenchyma. The image has a magnification factor of ×10. **b**, **c** These pictures represent the other 2 metastatic tumors with exophytic growth. The images have a magnification factor of ×2. **d** The urothelium in proximity (arrows) shows neither glandular metaplasia nor dysplasia. The image has a magnification factor of ×20. **e–g** The tumor cells express in a diffuse fashion CK20, CDX2, and beta-catenin, respectively. Regarding the latter one, no nuclear staining was experienced. The images have a magnification factor of ×4, ×8, and ×40, respectively. **h** The hot spots of exon 2 of the *KRAS* gene (codons 12–13) were amplified by PCR, and the nucleotide sequence was determined by Sanger capillary sequencing. The sequencing identified a G12D (c.35 G > A) mutation, one of the most common mutations. The figure indicates the representative sequence of the ureter metastasis.

to primary urinary tract neoplasms, hematuria was noticed. It is important to note that the metastatic involvement of the ureter is usually asymptomatic. In symptomatic cases, the signs are often nonspecific, like back pain, dysuria, frequent urination, etc. [4].

In the sigmoid adenocarcinoma resected, there was an extensive lymphovascular invasion along with a broad tumor budding. Although the exact mechanism and risk factors are still not characterized, we suggest that the invasive nature of the primary tumor may explain the development of this ureteral metastasis through the rich lymphatic network of the periureteral soft tissue.

A metastatic spread to the renal pelvis is an extraordinary phenomenon with solely anecdotal cases reported, and the lung is the most important site for the primary tumor [9]. In our case, 3 metastases were identified in the renal pelvis, and among the ureteral and renal pelvis tumors, apart from flattening and thinning, the urothelium was intact. Considering the link between these changes, first, we should speculate on a further lymphatic spread of the ureteral tumor toward the renal pelvis. However, all sections of the ureter have their transverse lymphatic circulation, so dissemination from the distal part of the ureter to the renal pelvis seems impossible. Second, it is a well-known and accepted fact that renal pelvis UCC might involve the distal region of the urinary tract by drop metastasis [10]. Also, there are reports on drop metastasis from renal cell carcinoma to the distal part of the genitourinary system [11]. In our patient, the ureter tumor caused an obstruction leading to hydroureter and hydronephrosis, and we hypothesize that a reflux mechanism was responsible for the tumor cell seeding and implantation. Also, it was earlier demonstrated that the previously traumatized urothelium was more vulnerable to drop metastasis [12].

Cystoscopy is the standard procedure in patients with assumed bladder cancer, while ureteroscopy can access the upper urinary tract [13]. Concerning the latter one, rigid and flexible devices are available. Rigid ureteroscopy provides a better perceptibility and enables the use of supplementary components, but the entry to the ureter is sometimes problematic or even impossible [13]. Flexible ureteroscopy can be an alternative; however, these devices are more expensive and need additional instruments [13]. Both technics may provide a solid diagnosis of the underlying condition; furthermore, a curative surgical resection might be performed or biopsy samples may be harvested for histological examination [13]. Also, these samples are fit for biomarker testing (i.e., PD-L1 immunohistochemistry) or genetic analysis. On the other hand, urine cytology is an alternative to detect or screen urinary tract cancer. Most frequently, voided urine is used because this is the easiest to obtain, but the sample is usually paucicellular [13]. For cytological analysis, instrumented urine or urine from ileal conduit can be investigated as well. Regarding the former one, cellularity is usually appropriate, although instrumentation artifact may lead to a false-positive result [13]. In general, urine cytology is an adequate and sensitive diagnostic tool for high-grade tumors, but it is less sensitive for low-grade lesions [13]. Of note, by applying additional technics like UroVysion FISH, the sensitivity can be improved [13]. In our case, the rigid ureteroscopy was not successful; thereby, no pathological diagnosis was established before the ureteronephrectomy.

From a pathological standpoint of view, in our case, the main differential diagnostic consideration was the primary adenocarcinoma of the ureter and the renal pelvis. This kind of tumor is mostly diagnosed in the urinary bladder and exceedingly rare in the sites mentioned above [14]. Also, the diagnosis of the primary adenocarcinoma in the urinary bladder is usually made by exclusion since no specific markers for the distinction from metastatic CRC exist [15]. Some authors suggest the use of β-catenin staining due to lack of nuclear expression in primary urinary tract adenocarcinoma [16]; however, in our case, β-catenin was useless because both the primary and metastatic tumors showed a membranous positivity pattern. Conventional markers like CK7, CK20, GATA3, and CDX2 also have limited diagnostic value [15].

On the other hand, nearby the primary urinary tract adenocarcinoma, glandular metaplasia may be present in the urothelium; therefore, a comprehensive sampling and a careful investigation of the adjacent urothelium is advised [17]. In our case, the entire ureter was processed, and the changes as mentioned earlier were experienced neither in the ureteral tumor nor in the renal pelvis metastases. If the histological material is suitable, genetic testing might be a reliable tool for distinction. Notably, molecular tests have the best accuracy when the known mutation of a primary tumor is looked for. The genetic background of the UCC is extensively investigated and documented, but, in contrast, the genetic landscape of urinary tract adenocarcinomas is less known. Earlier, low-frequency *KRAS* and *TERT* promoter region mutations were identified in urinary tract adenocarcinomas, and there are reports on alterations

of *TP53*, *RB1*, *PIK3CA*, and *RB1*, too [18]. Of note, the genetic changes described partly overlap with UCC and CRC, but their frequency varies. For instance, *TERT* promoter region mutation is present in approximately 80% of bladder UCC cases; however, it is found only in 13%–28.5% in bladder adenocarcinomas [18]. Also, approximately 30%–40% of CRC shows *KRAS* mutation, while up until now, in bladder adenocarcinoma, an 11.3% frequency was described [18, 19]. Additionally, KRAS and NRAS are routinely investigated before anti-EGFR therapy in metastatic CRC; therefore, we ordered a KRAS testing of the ureteral tumor. In our case, molecular testing was particularly useful because the same pathogenic mutation of the *KRAS* gene was identified in every tumor tissue sequenced. As stated earlier, there are some reports on *KRAS* mutation in urinary tract adenocarcinoma [18]. However, in our case, all the samples investigated (primary colorectal carcinoma, ureteral tumor, 3 renal pelvis tumors, and lymphatic metastasis) harbored the same mutation, and the chance to exist the same mutation in 4 different tumors seems to be dubious. Besides the abovementioned genetic alterations, primary urinary tract adenocarcinoma may harbor microsatellite instability that can be investigated by immunohistochemistry or PCR testing [20]. In our case, we used MLH1, MSH2, MSH6, and PMS2 immunostainings, and there was a strong retained expression of all the proteins mentioned above in the tumor cells; thus, the tumor was microsatellite stable. In the differential diagnosis, UCC with glandular differentiation should be regarded too. However, first, this feature usually presents in up to approximately 10–20% of the cases, and second, the glandular component is found within the conventional UCC. Last, these tumors are normally characterized by a strong CK7 positivity along with a variable CDX2, SATb2, and Cadherin17 expression [21]. The histological appearance and the immunoprofile of our case were not in harmony with the previous features, and therefore UCC with glandular differentiation was excluded.

Metastatic adenocarcinoma of the urinary tract could show various histological features depending on the primary tumor type; therefore, the clinical data obtained on any previous malignancy are crucial for the diagnosis [6]. It is also necessary to use the immunohistochemical markers in combination. According to our practice, an antibody panel containing CK7, GATA3, CK20, PAX8, TTF1, CDX2, and NKX3.1 (for males) or mammaglobin (for females) seems to be suitable for covering not only UCC but also the most frequent metastatic adenocarcinomas.

In conclusion, we presented a case of coexisting ureteral and renal pelvis metastases coming from colon adenocarcinoma. This is the first case reported with such a unique constellation in metastatic CRC to the best of our knowledge. Its distinction from the primary adenocarcinoma of the urinary tract is essential to reach excellent patient care. Although molecular genetic testing can be of limited value, DNA sequencing might be a powerful diagnostic tool in well-selected cases.

Statement of Ethics

This study was conducted with the permission of the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged (No. 188/2019-SZTE). The patient gave his written informed consent for the publication of all data and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Z. Fejes prepared the figures and wrote the manuscript. I.E. Király, Á.M. Fehér, P.G. Kovács, and L. Torday provided the patient characteristics and follow-up data. Z. Gyuris and F. Sükösd performed the histological and genetic analysis. L. Kuthi contributed to study concept and final supervision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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