

Case Report

Simultaneous Urothelial Carcinoma in the Upper Urinary Tract and Contralateral Renal Cell Carcinoma: A Case Report

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Keywords

Contralateral · Molecular-targeted drug · Renal cell carcinoma · Simultaneous · Urothelial carcinoma

Abstract

Introduction: Although urological surgeons often diagnose cases of simultaneous double cancers of the urinary tract in our clinical practice, few reports have shown that treatment strategies achieve both anticancer effects and preservation of renal function for simultaneous contralateral renal cell carcinoma and urothelial carcinoma. Although there are many options for the treatment of renal cancer, such as immunotherapy and - drugs, and many surgical procedures, such as laparoscopic surgery and robot-assisted surgery, no treatment strategy has been established for double cancer of the bilateral urinary tracts. We encountered a case in which contralateral renal surgery was performed under a precise preoperative plan; as a result, the introduction of dialysis could be avoided, and the anticancer effect could be maintained.

Case Presentation: A 73-year-old man was diagnosed with contralateral left renal cell carcinoma and right ureteral cancer. Initially, the patient underwent laparoscopic radical nephroureterectomy for right ureteral urothelial carcinoma. Subsequently, robot-assisted laparoscopic partial nephrectomy for left renal cell carcinoma was performed after treatment with the molecular-targeted agent, pazopanib. Even after partial nephrectomy, renal function was maintained, and dialysis was avoided. **Conclusion:** In cases of simultaneous renal cell carcinoma and contralateral ureteral cancer, it is possible to preserve both anticancer effects and renal function using careful treatment strategies.

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Introduction

Since the report by Billroth [1] in 1879, many reports of double cancers, including gastrointestinal and urinary cancers, have been published with progress in diagnostic imaging. Double carcinomas with simultaneous renal cell carcinoma (RCC) and contralateral upper urinary tract urothelial carcinoma (UC) are extraordinarily rare [2]. To the best of our knowledge, only 27 cases have been described worldwide. In addition, there is still no clear treatment strategy to achieve both anticancer effects and the preservation of renal function. Here, we report a case in which both renal surgeries were performed under careful planning; as a result, the need for dialysis was avoided and the anticancer effect could be maintained.

Case Presentation

The patient was a 73-year-old male with no significant complaints. His personal history revealed no factors, such as smoking, obesity, or exposure to industrial chemicals, associated with an increased risk of RCC and UC. He had no notable family history of cancer. His medical history included hypertension, diabetes, dyslipidemia and angina. He was referred to our hospital as a left kidney tumor was identified on ultrasonography during regular medical checkups.

Contrast-enhanced computed tomography (CT) revealed a solid tumor 15 mm in diameter in the right lower ureter and a solitary hypervascular tumor 55 mm in diameter in the left kidney (Fig. 1). Urine cytology revealed high grade UC. Right retrograde pyelography was performed, and the ureteral tumor was biopsied under ureteroscopy (Fig. 2). Pathological findings of a ureteral tumor biopsy revealed a grade 2 papillary UC. If surgical treatment is delayed and the cancer progresses and metastasizes, we consider the possible drug treatment options and prognosis. As a result, we decided to perform surgery for UC, which could have a poorer prognosis, prior to surgery for RCC. The patient underwent laparoscopic right total nephroureterectomy (LUN) as the first-line treatment for right ureteral urothelial cancer. Pathological findings of the LUN revealed invasive UC (G2 > G3), pT1.

Creatinine changed from 1.00 to 1.62 mg/dL, and the estimated Glomerular Filtration Rate changed from 59.7 to 33.5 mL/min/1.73 m² before and after surgery. Renal function decreased to approximately 60% of that before LUN. Although radical nephrectomy is considered a highly curative treatment for clinical T1b renal cancer, nephron-sparing surgery and partial nephrectomy were considered because dialysis cannot be avoided. The patient also had a strong desire to avoid dialysis. Thus, we first introduced treatment with a tyrosine kinase receptor inhibitor (TKI) to reduce the resected kidney volume as much as possible. First, we chose pazopanib preoperatively because of its high tumor shrinkage rate, improved prognosis, and fewer side effects, including renal dysfunction [3, 4]. Even in the absence of distant metastasis, the use of pazopanib is covered by insurance in Japan if the patient has RCC that cannot be completely resected, and there are no insurance-related disadvantages. Although we administered pazopanib at a dose of 800 mg daily, treatment was discontinued because of hypertension and severe diarrhea after 1 month. Second, axitinib (10 mg daily) was administered for 4 months. Subsequent CT showed approximately 20% tumor shrinkage from 55 to 42 mm in left kidney, owing to sequential therapy with TKIs (Fig. 3). We decided that robot-assisted laparoscopic left partial nephrectomy (RAPN) would be adaptable and feasible instead of radical nephrectomy because tumor shrinkage was achieved by treatment with TKIs. The RENAL score was 7 (2-2-2-p-1), which was an intermediate risk. Left RAPN was performed, and the surgery was completed as planned without any problems. The pathological findings were clear cell RCC, grade 1, pT1b.

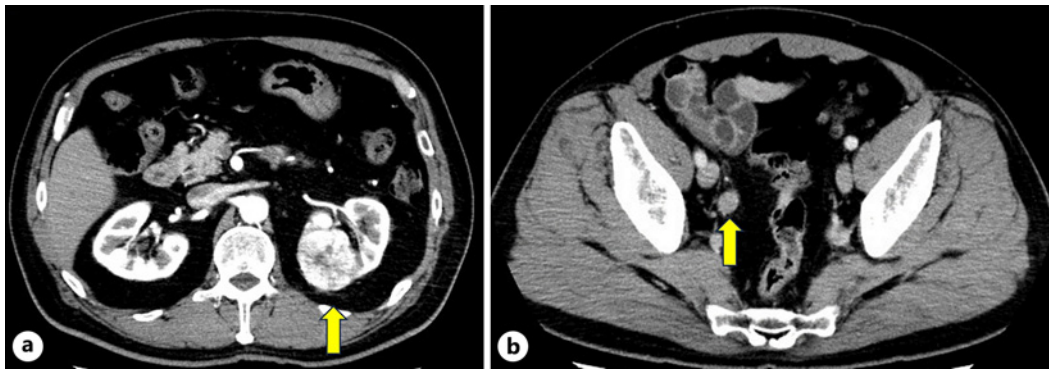


Fig. 1. Contrast-enhanced computed tomography (CT) scan. **a** Solitary renal cell carcinoma (RCC) on axial CT images. A hypervascular RCC, approximately 55 mm in diameter, was found in the left lower pole of the kidney. **b** A lower ureteral tumor in axial images of CT scan. A urothelial tumor (approximately 15 mm in diameter) was observed on the right side of the lower ureter.

After RAPN, the postoperative laboratory data showed an elevated creatinine of 1.81 from 1.62 mg/dL and a declined estimated glomerular filtration rate of 29.7 from 33.5 mL/min/1.73 m². Renal function was only reduced by approximately –10% compared to before RAPN. Therefore, the patient did not require hemodialysis after surgery and did well thereafter. More than a year later, the patient had no cancer recurrence or renal function deterioration.

Discussion

Most studies on simultaneous RCC and UC of the upper urinary tract have been described in case reports or small series. Owing to the rarity of the disease and limited reports, treatment strategies for simultaneous RCC and UC of the upper urinary tract remain uncertain. Simultaneous RCC and ureteral carcinoma have been reported in chronic hemodialysis patients, which may imply an increased susceptibility to urological malignancy in these patients [5]. However, none of these were verified as specific risk factors for the simultaneous presence of tumors. In the treatment of contralateral RCC and UC, it is important not only to cure the double cancer, but also to preserve renal function. In general, the UC that develops in the renal ureter has many recurrences in the residual ureter, and considering the multicentric development of UC, UC side is treated as a total nephroureterectomy. Therefore, the kidney on the side where the cancer occurred cannot be preserved. Partial nephrectomy is recommended for contralateral RCC [6–8].

In ureteral tumors, conservative management has been discussed in low-risk cases and allows the sparing of morbidity associated with radical surgery without compromising oncological outcomes or kidney function [9]. The 2015 European Association of Urology (EAU) guidelines suggest that conservative management may be considered when the tumor is unifocal, small (<1 cm), and low-grade, with no evidence of an infiltrative lesion on CT urography. Referring to the current EAU guidelines, and in this case, in order to preserve the kidney on the side with ureteral cancer, distal ureteral resection ± vesicoureteral neostomy was also one treatment option for distal ureteral cancer. However, when performing retrograde pyelography, it was not possible to biopsy the renal pelvis mucosa upstream of the relatively large ureteral cancer, thus it was not possible to rule out the possibility of CIS lesions upstream of the tumor. In this case, the ureteral tumor was relatively large at 1.5 cm, and the

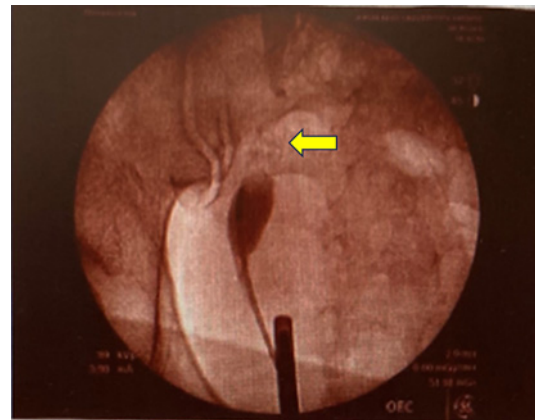


Fig. 2. Right retrograde pyelography (RP). A contrast-enhanced defect image of approximately 3 cm suggests UC of the lower ureter.

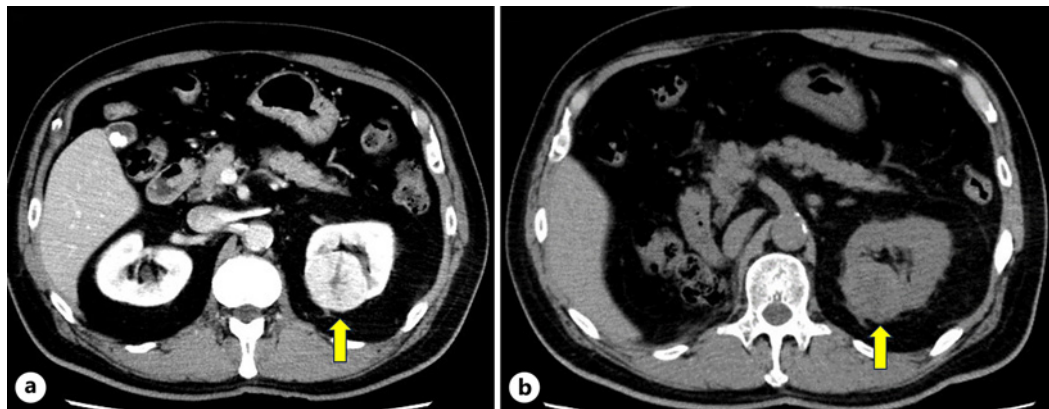


Fig. 3. CT images before and after treatment with tyrosine kinase inhibitors (TKI), pazopanib, and axitinib. **a** Axial CT images of RCC before treatment with TKIs. The diameter of the renal tumor in the lower left pole of the kidney was estimated to be 55 mm. **b** Axial CT images of RCC after tyrosine kinase inhibitor treatment with TKIs. The renal tumor diameter decreased significantly from 55 to 40 mm after treatment with molecular-targeted drugs.

nuclear atypia grade was grade 2 on biopsy, and in addition, the patient tested positive for UC on natural urine cytology. Therefore, considering the possibility of a curative operation, we decided that a radical nephroureterectomy would be preferable to a partial ureterectomy [10]. One report showed that in the case of RCC and UC at almost the same clinical stage, treatment of UC should be prioritized because UC generally has a worse prognosis than RCC [2]. In this case, similar to this idea, we also judged that the prognosis of UC was worse than that of RCC and prioritized total nephroureterectomy. However, there are no reports of simultaneous UC of the upper urinary tract or contralateral RCC treated with TKIs. There is limited or no strong evidence supporting the use of TKIs as a neoadjuvant treatment for RCC. However, a meta-analysis showed that neoadjuvant treatment reduced the operation time and resulted in a greater proportion of patients choosing partial nephrectomy [11]. We determined that if tumor shrinkage was achieved, partial nephrectomy would be possible, and dialysis could be avoided. Pazopanib was selected as the first-line medication, considering its more effective features, such as the objective response rate, tumor shrinkage rate, and side effects. In the randomized phase III COMPARZ trial, pazopanib had an objective response rate of 31%, compared to 25% with sunitinib. The response was reported to be 17.4 weeks for

sunitinib and 11.9 weeks for pazopanib. Pazopanib is superior in terms of response rate and time to response [3]. It has been reported that the median tumor reduction rate was 26% after treatment with pazopanib for RCC, and there were no cases of disease progression [12]. In addition, in a clinical study in which pazopanib was used preoperatively for advanced RCC, an average tumor shrinkage of 14% was observed after approximately 3 months of pazopanib administration, and surgery was possible in 63% of cases [13]. Regarding the use of axitinib used as a second-line therapy in the current case, it has been reported that an average tumor shrinkage of 28.3% was observed after approximately 3 months of axitinib administration, with no cases of disease progression [14]. In this case, the tumor shrank by 20% after treatment with pazopanib for 1 month and axitinib for 4 months. TKIs are effective agents for preoperative tumor shrinkage.

Combination therapy with TKIs and immune checkpoint inhibitors (ICIs) is now available and is more effective in terms of objective response rate [15, 16]. Currently, the combined use of TKIs and ICI will become mainstream. Since avelumab has a lower risk of immune-related adverse events than other ICIs, the preoperative use of avelumab plus axitinib may be more beneficial [15].

We believe that management plans must be individualized. All factors, including the biological features of each tumor, bilateral renal function, and patient quality of life, should be considered together.

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Statement of Ethics

This study protocol was reviewed and approved by Juntendo University School of Medicine Ethics Committee for Medical Research, Approval No. F24-0021. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000542059>).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.I. drafting of the manuscript; M.N. and S.H. supervision; M.T., O.M., H.H., S.I., H.I., and F.S.: acquisition of data.

Data Availability Statement

This case report is publicly available on legal or ethical grounds because written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Further inquiries can be directed to the corresponding author. The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from S.H. (shorie@juntendo.ac.jp) upon reasonable request.

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