Bladder metastasis from type 2 papillary renal cell carcinoma: A case report

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Abstract. Renal cell carcinoma (RCC) is a common urinary tumor that may be pathologically divided into different subtypes: clear cell RCC, papillary RCC (PRCC) and chromophobe RCC. The most common organs of RCC metastasis are the lung, liver and bones, while bladder metastasis is rare. The treatment for PRCC metastasis is also a problem due to limited clinical data. Therefore, every single case of PRCC metastasis may significantly contribute to establishing a standard treatment protocol. The present study reported on a patient who suffered from repetitive bladder PRCC metastasis with 1.5 years of follow-up. A 54-year-old male patient was diagnosed with left renal pelvic carcinoma in March 2020 and underwent a laparoscopic radical nephroureterectomy of the left kidney. The postoperative histological examination revealed that the tumor was consistent with a type 2 PRCC. Bladder metastasis was discovered three months after the surgery and transurethral resection of the bladder tumor (TURBT) was performed to eliminate the tumor in the bladder. Only three months after the initial TURBT, bladder metastasis was detected again, combined with lung metastasis. The patient refused to undergo radical cystectomy. Therefore, a second TURBT was arranged and targeted drugs were administered. However, both bladder and lung metastases were insensitive to the treatment strategy applied, although immunotherapy was subsequently added. The patient died in October 2021 due to respiratory failure and cachexia. The report aims to provide the whole treatment progress and lessons learned from this case, which is relatively rare.

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Introduction

Renal cell carcinoma (RCC) is the seventh-most common cancer type in males and the tenth-most common cancer type in females, with an estimated 50,290 new cases in the US alone in 2021 (1,2). Papillary RCC (PRCC) is the second-most common heterogeneous cancer, accounting for 15% of all kidney cancers (3). PRCC may be morphologically subdivided into types 1 and 2, and the latter usually has a poorer prognosis than the former (4). It has been reported that among all patients with RCC, only 20-30% experience metastasis (5). Furthermore, RCC commonly metastasizes to the lung (50-60%), liver (30-40%), bone (30-40%) and regional lymph nodes (40-60%), among which the bladder is a rare site of metastases (only 2%) (6,7). Therefore, bladder metastasis of type 2 PRCC is uncommon and rarely reported. The present study reported the case of a 54-year-old male patient with a 6-month history of a dull ache in the left part of the waist and gross hematuria. The patient had undergone computed tomography (CT) and ureteroscopic biopsy before being admitted to our hospital (the First Affiliated Hospital of Sun Yat-sen University). Physical examination revealed no obvious abnormality. Voided urine cytology indicated the presence of tumor cells; however, the histological type of the tumor cells was unclear. The fluorescence *in situ* hybridization (FISH) chromosome variation detected by the p16/CSP3/CSP7 combination probe, indicating malignancies in the collective system. The patient underwent a series of surgical treatments, including radical nephroureterectomy, transurethral resection of bladder tumor (TURBT) and systemic therapy. The patient experienced recurrent type-2 PRCC and the outcome of the combination treatment was modest. In the end, the patient died 1.5 years later due to multiple organ failure caused by multiple organ metastasis.

Case report

Chief complaints. A 54-year-old male patient was admitted to the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) with a 6-month history of a dull ache in the left part of the waist and gross hematuria.

History of present condition. The patient was initially admitted to a local hospital (Meizhou Hospital of Traditional Chinese Medicine, Meizhou, China) in March 2020 with a

6-month history of a dull ache in the left part of the waist, gross hematuria and urinary irritation. Prior to admission, the patient did not receive any treatment. Soon after the admission, a series of symptomatic treatments and examinations, including computed tomography (CT) and ureteroscopic biopsy combined with double J tube insertion, were performed to make an initial diagnosis. The ureteroscopic biopsy was performed after acquiring consent from the patient; it has a certain risk of causing implantation metastasis through the ureter. The pathological examination revealed moderate to severe dysplasia of the urothelium, which required to be further differentiated from urothelial carcinoma. The patient decided to further turn to the Department of Urology of the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) for further clinical treatment based on the results.

Past medical history. The patient had a history of left kidney stones and underwent percutaneous nephrostomy and left percutaneous nephrolithotomy in 2018. In addition, the patient had a 10-year history of hypertension and was taking amlodipine daily to control his blood pressure. The patient denied a history of smoking.

Physical examination. On admission to the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China), the patient's body temperature was 36.5˚C, the heart rate was 76 bpm, respiratory rate was 17 breaths/min and blood pressure was 133/77 mmHg. The abdomen was supple, without any masses or organomegaly, and no renal tenderness or percussion pain were observed.

Laboratory examination. Routine blood tests revealed a red blood cell count of $4.37x10^9$/l (normal range, $4\text{-}10x10^9$/l) and a hemoglobin level of 130 g/l (normal range, 120-160 g/l). None of the parameters was abnormal. Prothrombin and partial thromboplastin times were regular. Blood biochemistry test results were within normal ranges. The patient's serum creatinine level was 136 μmol/l and his blood urea nitrogen level was 6.4 mmol/l, demonstrating normal renal function. Voided urine cytology indicated the presence of tumor cells; however, the histological type of the tumor cells was unclear. FISH analysis (8) revealed chromosome variation detected by the GLP p16/CSP3/CSP7 combination probe.

Imaging examination. During the patient's stay at a local hospital (March 2020), abdominal CT revealed a filling defect in the left renal pelvis with chronic inflammation of the left kidney. However, left renal pelvis biopsy revealed moderate to high-grade dysplasia of the urothelial tissue and did not rule out the possibility of urothelial carcinoma. After admission to the Department of Urology, the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China), a chest CT scan, as well as an enhanced abdominal CT scan, were performed, revealing no obvious abnormality in both lungs, multiple nodular dense shadows in the left renal parenchyma and soft tissue density shadows in the left collective system. Some of the tissues in the middle and lower segments of the left kidney exhibited slight enhancement. By contrast, those in the middle and lower part of the collective system displayed moderate enhancement (Fig. 1). A pathology consultation was held based on the previously obtained pathological sections of masses in the ureter (the plain sections were acquired from the Meizhou Hospital of TCM by the patient and then stained at the pathology laboratory of our hospital). Pathologists at our hospital further identified the tissues as malignant tumors with a high suspicion of urothelial carcinoma.

Final diagnosis. The final diagnosis of the present case was carcinoma of the left renal pelvis.

Treatment. A laparoscopic radical nephroureterectomy of the left kidney combined with hilar lymph node dissection was performed. The postoperative specimen was nephridial tissue measuring 14x10x9 cm and left hilar lymph nodes 3 cm in diameter. The tumor was grey-white and measured 11.5x8x5.5 cm. Histological examination, which was performed according to standard procedures, revealed that the tumor was consistent with a type 2 PRCC (stage pT1b; Fig. 2A-A1), and an intravascular tumor thrombus was found. However, the tumor did not invade the renal adipose capsule and no malignant tissue was found in the lymph nodes. The patient recovered uneventfully and was discharged from our department on the seventh postoperative day.

Outcome and follow-up. At three months after the surgery, routine abdominal ultrasound indicated a spherical protuberance (1.0 cm) into the left side of the bladder lumen, which was subsequently confirmed by CT and combined positron-emission tomography-CT, which also revealed a highly metabolic lymph node in the left renal hilum with no other focal hypermetabolism (Fig. 1D, D-1). Although there were multiple scattered small nodules in both lungs, none demonstrated hypermetabolism. To clarify the nature of the mass in the bladder lumen, the patient underwent TURBT and four weeks of intravesical therapy of epirubicin (40 mg per instillation), and pathology of the resected specimen indicated bladder metastasis of PRCC (Fig. 2B and C). After initial TURBT, gene sequencing was performed (3DMed Clinical Laboratory, Inc.), and the result revealed amplification of the cyclin D (CCND1) gene. According to the European Society for Medical Oncology (ESMO) guidelines, a targeted therapy protocol with pazopanib (1,000 mg orally QD) was arranged.

After three months of targeted therapy, a routine CT scan indicated local thickening with multiple calcifications in the left and top parts of the bladder wall (Fig. 1E-E1), accompanied by enlarged nodules in both lungs, which were most likely metastatic tumors (Fig. 1F). After a general discussion in our department, radical cystectomy and continuation of targeted treatment were recommended. However, due to concerns regarding a potential reduction in quality of life, the patient refused this suggestion. Therefore, a second TURBT was performed to remove the metastatic tumors in the patient's bladder as thoroughly as possible (Fig. 3A-F), and the postoperative pathological results still revealed PRCC (Fig. 2D-D1). After the second TURBT, the patient received four weeks of intravesical therapy of epirubicin (40 mg per instillation) and underwent regular follow-up examinations at our hospital.

During the 9-month follow-up, the patient underwent TURBT three times to eliminate new recurrent tumors and received the targeted drug (pazopanib 1,000 mg orally once a

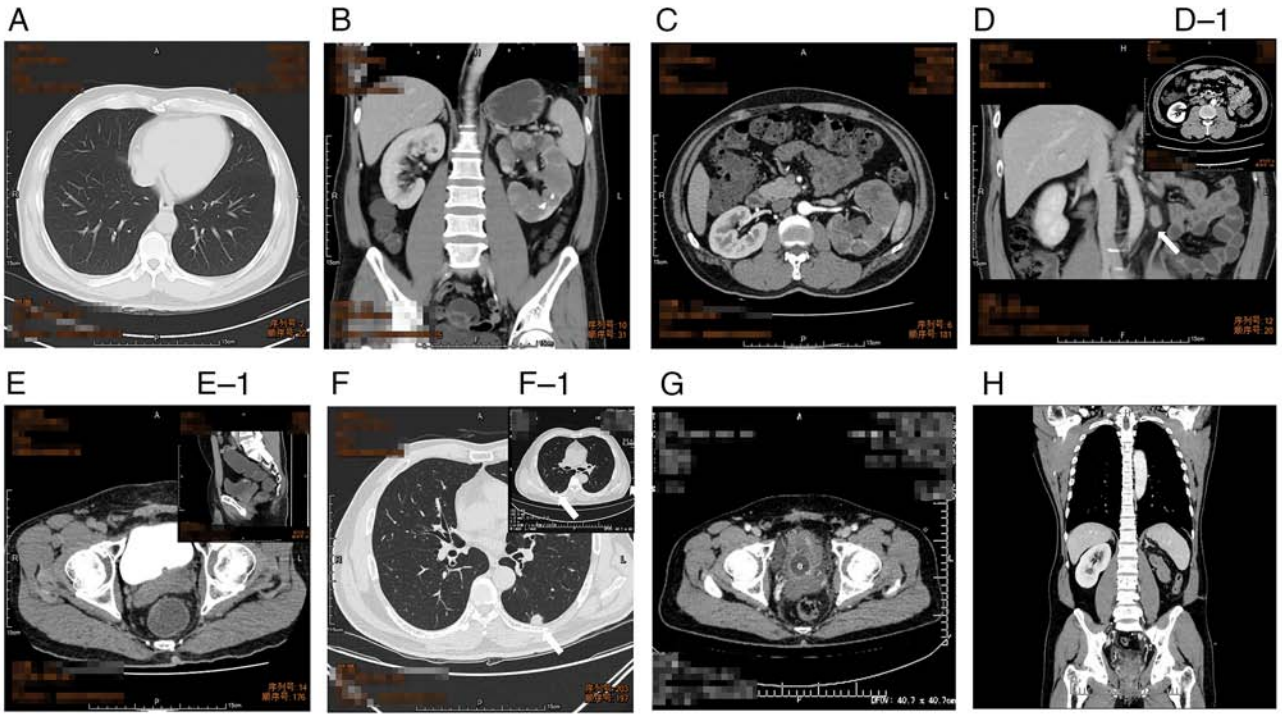

Figure 1. CT findings. (A) Initial chest CT scans indicated no obvious abnormality in both lungs. (B) Abdominal CT scan revealed dense nodular shadows in the left kidney and collective system. (C) Transverse section of the enhanced CT image revealed slight enhancement in the left kidney. (D) Routine CT scan indicated a sizeable metabolic lymph node near the left hilum three months after radical nephrectomy. (D-1) Transverse section of enhanced CT image of the enlarged lymph node. (E) Enhanced CT scan indicated a filling defect in the left bladder wall six months after radical nephrectomy. (E-1) Sagittal section of the CT scan revealed local thickening on top of the bladder wall. (F) Chest CT scan indicating enlarged nodules in both lungs with unique tumor features six months after radical nephrectomy (the figure only indicated a nodule in the left lung). (F-1) Chest CT scan indicating metastases in both lungs one year after radical nephrectomy (the figure only indicates a nodule in the right lung). (G) The follow-up abdominal CT scan revealed a solid mass that occupied most of the bladder and obscured the structure. (H) Coronal section of abdominal CT one year after the radical nephrectomy. CT, computed tomography.

day). However, after nine months, a CT scan revealed multiple recurrent tumors damaging the normal structure of the bladder (Fig. 1G and H) and new nodules in both lungs (Fig. 1F-F1), indicating the treatment effect of the drugs was modest. Therefore, immunotherapy with tirelizumab (200 mg administered every three weeks) was added. However, the antitumor efficacy was still unsatisfactory. Ultimately, the patient died in September 2021 due to multiple organ failure caused by multiple organ metastasis.

A flow chart is provided in Fig. 4 to briefly illustrate the entire treatment process of the patient.

Discussion

RCC is the most common renal malignancy in adults and has a high incidence of distant metastases (1). The most common organs of metastasis include the lungs, bones, lymph nodes and skin (9), while the bladder only accounts for approximately 2% of RCC metastases (7). Bladder metastasis of type-2 PRCC is rare, and only four cases have been reported (10-13). In the earliest case reported by Raviv *et al* (12), the patient received no adjuvant treatment after TURBT but conservative surveillance and was alive and free of disease six years after initial TURBT. In the study by Gajasinghe *et al* (10), the patient did not receive any adjuvant treatment until bladder metastasis was detected. Then, although she received interferon-alpha injections thrice a week, lung metastasis was subsequently developed. The patient survived at least six months after lung metastasis was diagnosed. However, it is reported that interferon-alpha has a low response rate (12%).

Babar *et al* (11) reported on a patient who was diagnosed with metachronous renal cell carcinoma and initially given sunitinib for systemic treatment. However, the patient did not tolerate the dosage of 25 mg; therefore, sunitinib was substituted with nivolumab. The patient died two years later after bladder metastasis was detected. However, in the most recent report by Kang *et al* (13), no detailed treatment schedule was mentioned. The treatment schedule of the present case partially referred to these previous reports.

Due to limited clinical data, there is currently no standard treatment schedule for PRCC and the existing treatment has largely been extrapolated from that of clear cell RCC (ccRCC). The present review summarized the experience gained from this rare case and certain potential mistakes were pointed out with the aim to provide new ideas for treating bladder PRCC metastasis.

Although targeted therapy and immune checkpoint inhibitors (ICI) have been widely utilized, surgery still has a crucial role in treating metastatic RCC (mRCC), which usually falls into two major categories: Cytoreductive nephrectomy and metastasectomy (MTS). Although the effect of MTS remains controversial, a recent systematic review has indicated that it could improve overall survival in patients who had previously undergone nephrectomy (14). Therefore, when suspicious metastasis was initially discovered during the follow-up of the present case, a TURBT was arranged. As previously

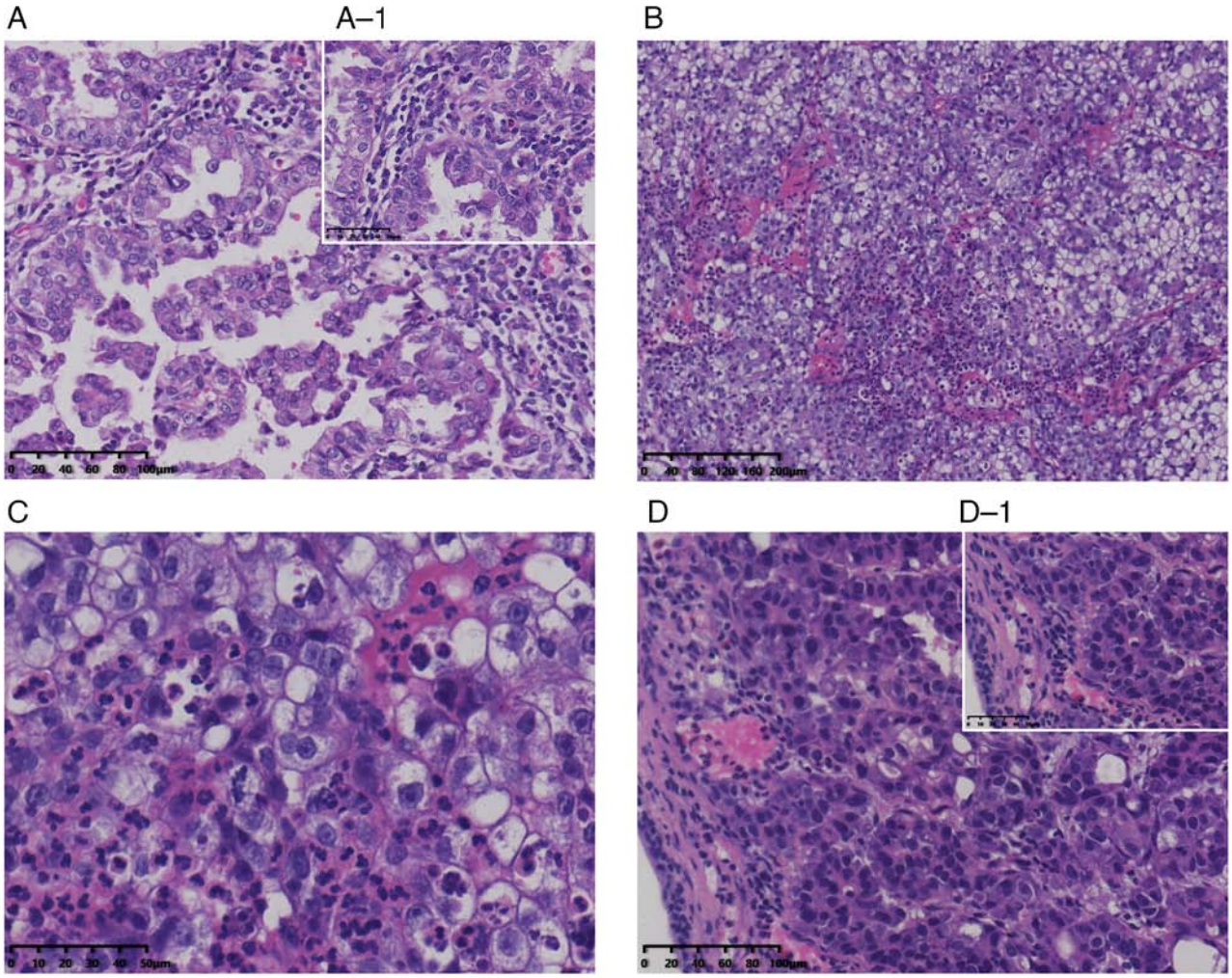

Figure 2. Pathological results. H&E staining of renal tumor and bladder metastases. (A) Histological examination of resected tumor in the left kidney revealed type 2 PRCC (magnification, x20). (A-1) The resected tumor in the left kidney (magnification, x40). (B) After initial TURBT, the pathological outcome revealed a mass of bladder metastasis of PRCC (magnification, x10). (C) Bladder metastasis of PRCC (magnification, x40). (D) Pathological outcome of the second TURBT revealed metastasis of PRCC in the bladder (magnification, x20). (D-1) Recurrent bladder metastasis of PRCC (magnification, x40) (H&E stain; scale bars, 200 μm). H&E, hematoxylin and eosin; PRCC, papillary renal cell carcinoma; TURBT, transurethral resection of the bladder tumor.

mentioned, the current treatment plan for papillary mRCC mainly refers to ccRCC or other similar diseases. Therefore, intravesical instillation with epirubicin (50 mg/50 ml, once a week for eight consecutive weeks and then once a month for 10 consecutive months) was arranged following TURBTs according to clinical experience and the patient was placed under observation, which is a strategy conventionally pursued in non-muscle invasive bladder cancer and has already been proven effective in eliminating residual tumor cells in the bladder after TURBT (14,15).

Intravesical RCC metastases are usually divided into two different types: Synchronous (present within 12 months after nephrectomy) and metachronous (present >12 months after nephrectomy), and the former correlates with an unfavorable prognosis (16). However, the mechanism of metastasis to the urinary bladder remains elusive. In general, four different hypotheses are suggested: i) Metastasis by dissemination through the urinary tract; ii) direct spread through the bloodstream via invasion of the renal vein; iii) metastasis through lymphatic vessels; and iv) retrograde perfusion due to embolism of tumor cells from the renal vein to its venous connections (17). In the present case, the metastases in the bladder were superficial. The patient was initially admitted to our hospital with a history of gross hematuria, which suggested a potential fracture of the renal pelvis. Therefore, drop metastasis may have been a significant route for tumor spread to the urinary bladder. By contrast, pathological analysis after nephrectomy revealed an intravascular tumor thrombus, indicating that retrograde tumor dissemination may have also had an important role in bladder metastasis in the present case. In the case of lung metastasis occurring only three months after bladder metastasis, a more radical treatment, namely radical cystectomy, should be considered when bladder metastasis was initially detected to decrease the metastasis rate and prolong the patient's survival time (1).

Sunitinib and pazopanib are both recommended targeted agents for non-ccRCC according to ESMO guidelines (1). Furthermore, a previous study revealed that pazopanib has similar efficacy to sunitinib with better safety and quality of life (18). Therefore, the latter was selected as the main drug in targeted therapy. Unfortunately, the effect of pazopanib in preventing tumor progression was modest. The insensitivity

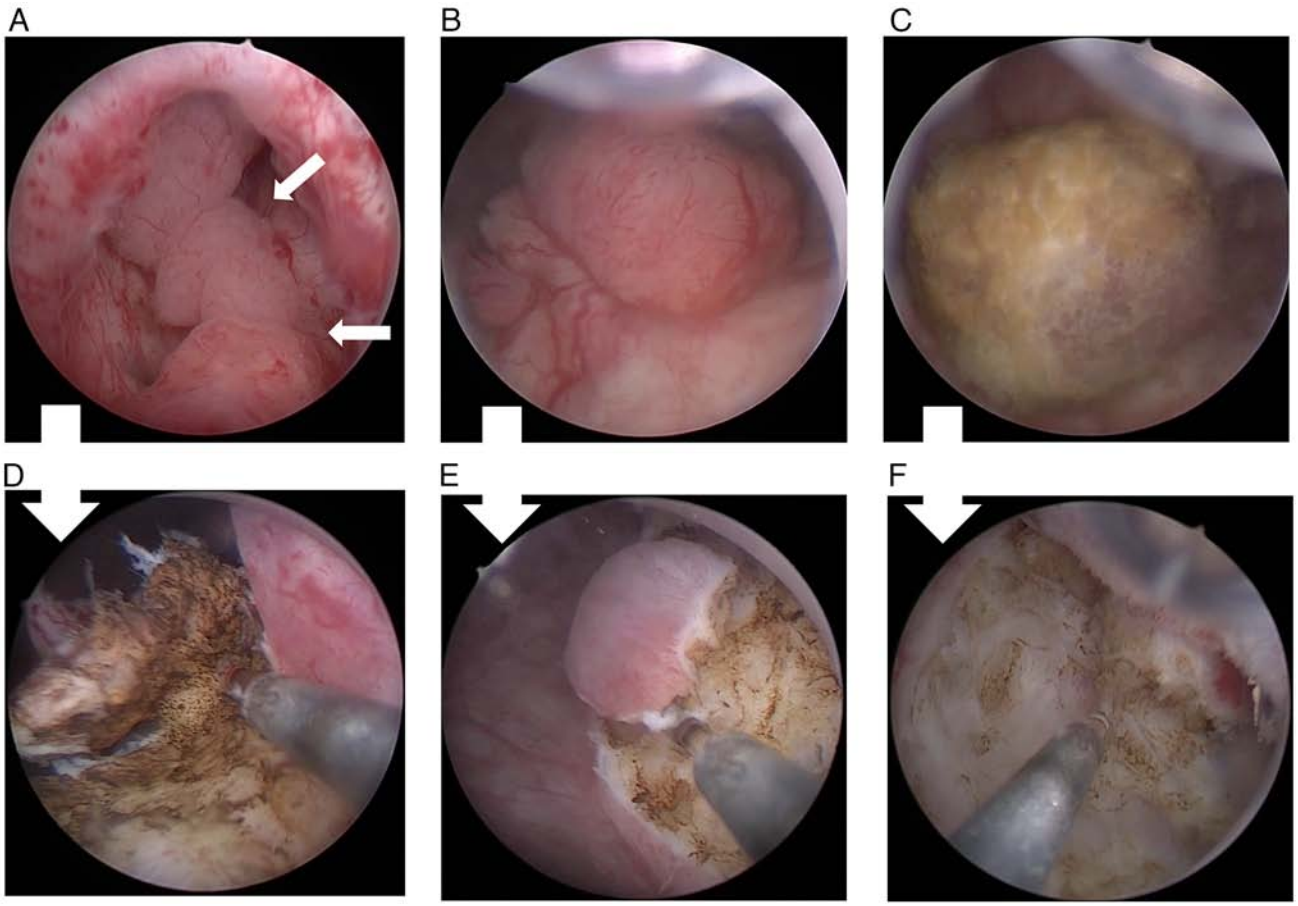

Figure 3. Intraoperative images. Resection of bladder tumor (thulium laser, 35 w). (A) Tumor in the vesical neck. The arrows indicate seminal hillock and tumor, respectively. (B) Multiple tumors in the wall of the bladder were close to the area of the original left ureterostoma. (C) Tumor in the posterior and top bladder wall with superficial calcification. (D) Tumors in the vesical neck were resected with a laser. (E) Tumors in the left wall of the bladder were resected with a laser. (F) Tumor in the posterior and top wall of the bladder was resected with a laser.

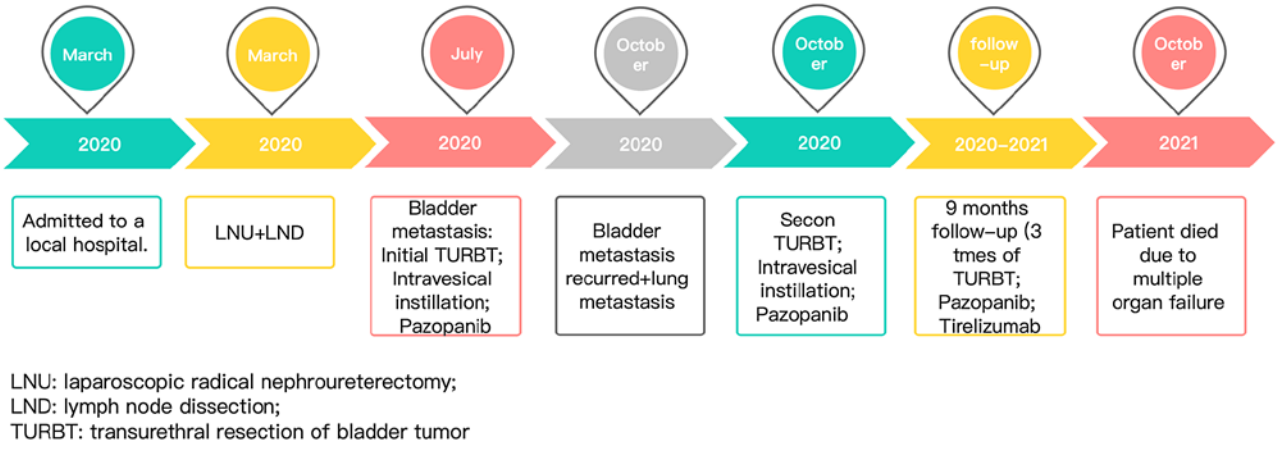

Figure 4. Flow chart. The whole treatment process of the patient. TURBT, transurethral resection of the bladder tumor; LNU, laparoscopic radical nephroureterectomy; LND, lymph node dissection.

of tumor cells to targeted agents may be the most important reason. Von Hippel-Lindau (VHL) gene mutations are closely related to RCC and cause the accumulation of hypoxia-inducible factors in cells and activation of downstream hypoxia-driven genes, including vascular endothelial growth factor (VEGF) (19). As a VEGF-receptor tyrosine kinase inhibitor, pazopanib may target and deactivate these downstream pathways, thereby achieving antitumor activity. However, VHL mutations are less frequent in patients with type 2 PRCC. Instead, mutations in the cyclin-dependent kinase (CDK) inhibitor 2A, CDK4/6 and MET genes are more common and are linked to other targeted therapies than pazopanib (20). The result of genetic testing also revealed amplification of the CCND1 gene, indicating the sensitivity of

the tumor to CDK4/6 inhibitors. Therefore, inhibitors of these genes, including foretinib, crizotinib and savolitinib, would likely show a better antitumor effect on PRCC than pazopanib, and the survival period of the patient may be further prolonged if treated with these drugs. However, the China Food and Drug Administration has not approved these drugs for treating patients with PRCC.

There were certain shortcomings in the treatment of the present case. First, a routine cystoscopy may have been performed prior to the laparoscopic radical nephroureterectomy, particularly when considering left renal pelvic carcinoma. However, the above-mentioned measure was not taken due to the negative result of the abdominal CT scan. It may be helpful to detect potential bladder metastasis early. Therefore, routine cystoscopy is recommended for type 2 PRCC when renal pelvis invasion is present. Furthermore, radical cystectomy should be performed decisively when bladder metastasis recurs. However, the patient of the present study refused this recommended treatment. The absence of radical cystectomy probably causes frequent recurrence and distant metastasis and affects the prognosis. In addition, ureteroscopic biopsy would have been feasible at the local hospital. However, a recent study revealed that ureteroscopic biopsy prior to radical nephroureterectomy may be associated with increased intravesical recurrence (21). As another limitation, adjustments for systematic treatment should be made depending on the therapeutic effect. In the case of the present study, genetic testing was performed and antitumor drug sensitivity was revealed. Although the effect was modest, out of concern regarding off-label drug use, the patient was always treated with pazopanib. However, there is currently no standard treatment protocol for bladder metastasis of PRCC due to its rarity. Therefore, it is bold to experimentally use those targeted drugs included in the drug-sensitivity table of PRCC but that are not standard agents permitted by the China Food and Drug Administration. Finally, there are several novel combination treatments for ccRCC, including immunotherapy combined with targeted therapy and targeted therapy combined with cryoablation (22). Although most of them were still in the clinical trial stage, these treatment strategies may have a reference function in treating nccRCC. Further large-scale prospective studies are still required.

In conclusion, bladder metastasis of type 2 PRCC is a relatively rare condition, with few reports and a lack of standard and effective treatment schedules. Decisive and radical metastasectomy may minimize the risk of distant metastasis. In addition, specific targeted agents and ICIs may have better effects in prolonging patients' survival than those with broad-spectrum antitumor activity. More case reports and systemic and large-scale studies are needed to guide clinical treatment of this condition.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

QZ: Conceptualization, revision and editing of the manuscript. SL: Writing-original draft, investigation, revision and editing of the manuscript. LWC: Writing-original draft, investigation. LZC: Conceptualization, supervision. JC: Conceptualization, methodology and supervision. QZ, SL and JC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Human Investigation Committee/Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) approved the present study. All procedures performed in this study involving the patient were in accordance with the 1975 Helsinki declaration and its later amendments or comparable ethical standards (approval no. 2020-420).

Patient consent for publication

The patient provided written informed consent regarding publishing his case data and images.

Competing interests

The authors declare that they have no competing interests.

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