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**Primary renal small cell carcinoma: A case report**

Xie K *et al*. Primary renal small cell carcinoma

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**Abstract**

BACKGROUND

Small cell carcinoma (SCC) is a malignant tumour that is frequently accompanied by extensive metastasis. Primary renal SCC has typical characteristics related to SCC and is extremely rare, with no uniform treatment standard. Clinical treatment is mainly based on the literature. Here we report the diagnosis and treatment of an interesting case of primary renal SCC.

CASE SUMMARY

We report a tortuous course of treatment for a 68-year-old man. Four years before diagnosis, the patient developed continuous gross haematuria, during which he underwent several ureteral biopsies, ureteral stricture relief, and urine exfoliated cell examinations; however, SCC was not confirmed. One month before radical resection of the renal pelvic carcinoma, the severe haematuria recurred. Computed tomography revealed transitional cell carcinoma in the right kidney and right upper ureter. A preoperative examination exluded the possibility of a pulmonary origin of the tumour, and primary renal SCC was diagnosed. The postoperative pathology findings were suggestive of SCC. The patient was treated with combined chemotherapy but died of tumour progression at 7 mo postoperative.

CONCLUSION

Our patient's disease onset in the context of a succession of regular testing and the fact that it occurred so quickly with perirenal encroachment immediately after diagnosis reveals the cruel and unforgiving side of the disease. Furthermore, patients with poor comprehensive treatment results require new treatment regimens.

**Key Words:** Kidney; Small cell carcinoma; Clinical features; Diagnosis; Treatment; Case report

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**Core Tip:** Our patient's onset in the context of a succession of regular testing, and the fact that it occurred so quickly, with perirenal encroachment immediately after diagnosis, reveals the cruel and cunning side of the disease. Futhermore, patients with poor comprehensive treatment results, proving the need to develop new treatment regimens.

**INTRODUCTION**

Small cell carcinoma (SCC) usually arises from the lungs, and extrapulmonary SCC accounts for 2.5%-5% of all SCC cases[1]. SCC occurs in the urinary system is extremely rare, and most commonly occurs in the bladder[2]. Primary renal SCC is even rarer. The rarity, aggressiveness, and poor prognosis of these tumours adds to the seriousness of the disease[3]. The overall survival rate of renal SCC is worse than that of pulmonary SCC[4,5]. Given the very aggressive behaviour of renal SCC, standard treatments are required[5]. Here we report a case of primary renal SCC and discuss its rapid clinical progression, treatment, and long-term effects.

**CASE PRESENTATION**

***Chief complaints***

Right low back pain, abdominal distension and repeated gross hematuria for 2 wk.

***History of present illness***

The patient was a 68-year-old man admitted to The First Affiliated Hospital of Nanchang University on September 20, 2020 with a 2-wk history of right waist pain and abdominal distension with repeated gross haematuria. No special observation was noted during physical examination.

In August 2016, the patient was admitted to our hospital with repeated gross haematuria. Computed tomography (CT) showed thickening of the wall of the lower part of the right ureter suggestive of ureteral cancer, hydronephrosis of the right kidney and upper and middle ureteral segments, and right renal insufficiency. After consultation with the patient and his dependents, we decided to perform a ureteral tumour biopsy, and postoperative pathology exhibited a limited lower segment of the right ureter, suspected to be cancerous. Immunohistochemistry showed CD20 (+ mainly umbrella cells, focal whole layer +), Ki-67 (+ mainly basal cells), and p53 (-) (Figure 1A). We recommended a radical ureterectomy for this cancer; however, the patient and his family refused, and he agreed to undergo ureteral bladder replantation to treat distal ureteral strictures (right) 1 wk after the biopsy (right). Intraoperative frozen pathology and postoperative pathology of the vesicoureteral junction revealed chronic mucositis and mild atypical hyperplasia of the local urothelium (Figure 1B).

The patient’s postoperative recovery was good, but irregular gross haematuria was observed during the follow-up period. Re-examination with CT in our hospital in January 2017, March 2019, and September 2019 showed postoperative changes in the lower segment of the right ureter and slight hydronephrosis in the right kidney and upper ureteral segment. A ureteral biopsy was performed again in 2019 for gross haematuria, and the postoperative pathology findings were consistent with the morphological manifestation of a right ureteral polyp (Figure 1C). Urine exfoliative cytology was performed in August 2016 and March 2019, but the results were negative. The remainder of this paper is nothing special.

***History of past illness***

The patient had no relevant medical history.

***Personal and family history***

The patient had no relevant personal or family history.

***Physical examination***

The patient’s vital signs were normal. There is percussion pain in the right renal area, normal on the left side.

***Laboratory examinations***

The patient’s creatinine level was 114.1 μmol/L and urea nitrogen level was 4.9 mmol/L. The glomerular filtration rate (GFR) of the left kidney was 31.88 mL/min, while that of the right kidney was 14.38 mL/min. The remaining participants were not special.

***Imaging examinations***

B-mode ultrasound showed the following: (1) Hydronephrosis of the right kidney suggestive of possible middle and lower ureteral obstructions; and (2) Benign prostatic hyperplasia with calcification. CT showed the following: (1) A soft-tissue tumour of the right kidney and right upper ureter segment suggestive of transitional cell carcinoma in addition to multiple enlarged lymph nodes in the right renal hilum suggestive of metastasis; (2) Blood perfusion and excretion function of the right kidney were significantly decreased; (3) Postoperative changes in the right ureter. The wall of the lower part of the right ureter near the entrance of the bladder was slightly thickened and enhanced. Therefore, an endoscopic examination was recommended; and (4) The presence of multiple nodes in both lungs suggested the possibility of metastasis (Figure 2).

**FINAL DIAGNOSIS**

The postoperative pathology showed 60% high-grade invasive papillary urothelial carcinoma with 40% SCC in the right kidney, nervous invasion, visible tumour thrombus in vessels, and invasion of the renal parenchyma. No cancer was noted in the ureteral stump or perirenal fat. Immunohistochemistry showed GATA-3 (nest group +, flake -); CK7 (nest group +, flake -); p63 (nest group +, flake -); CGA (nest group -, flake +); syn (nest group -, flake +); CD56 (nest group -, flake +); CK20 (-); NSE (-); Ki-67 (nest group 60% +, flake 90% +); and CK (nest group strong +, flake weak +). Microscopic examination of the right lower ureter revealed lumen dilation, a partial epithelial defect, partial coverage with urothelium, and severe mechanical injury to the focal epithelial cells affecting the observation. There were two right renal pedicle lymph nodes, but no cancer metastasis was found (0 take 2). Primary renal SCC of the right kidney was also considered (Figure 3).

**TREATMENT**

The preoperative diagnosis was renal pelvic carcinoma, and Laparoscopic radical resection of the tumour was performed in October 2020.

**OUTCOME AND FOLLOW-UP**

Combined with the relevant guidelines and literature recommendations, we recommended that the patient start GP chemotherapy 1 mo after surgery, such as gemcitabine 1000 mg/m2, D1 and D8 intravenous drip, and carboplatin 80 mg/m2 D1-3 intravenous drip as a 21-d cycle. The dosage would be adjusted after each cycle according to the change in the patient's body surface area. Moreover, a regular monthly review of CT scans enables observation of the changes in the disease (in January, CT examinations were not performed due to the serious epidemic situation of the novel coronavirus, but chemotherapy was still performed on schedule). CT showed tumour metastasis in the lungs and liver in December, and the mediastinum seemed to occupy space. From December to February, the space occupation of the lung seemed to improve, while the liver metastasis became increasingly serious and there was no significant change in the mediastinum. The examination in March showed that the occupation of the lung, liver, and mediastinum had increased, and there was a new mass in the right kidney area of the original operation. In April, metastatic tumours developed rapidly (Figure 2). Other than fatigue and emaciation, the patient did not experience any other discomfort and the chemotherapy drugs were not rejected. During this period, we suggested to the patient and his family that we change the chemotherapy method and add radiotherapy, immunotherapy, and other therapies according to the changes in his condition; however, the idea was rejected and he continued the original treatment plan. When the six cycles of chemotherapy were completed, we suggest that he receive further treatment, but he and his family refused. On May 5, he died of multiple organ failure.

**DISCUSSION**

The incidence of renal SCC is low, and studies and reports worldwide are rare[6]. We incompletely counted 92 globally published cases of renal SCC from 1984 to 2022 and summarized their clinical characteristics and treatment options (Table 1). The common clinical manifestations of renal SCC are not significantly different from those of other renal parenchymal malignant tumours and include low back pain, haematuria, abdominal mass, abdominal discomfort, weight loss, and swelling of lymph nodes on the body surface[7]. In addition, it is unrelated to paraneoplastic syndromes[8]. To date, only one case was reportedly associated with a syndrome of inappropriate antidiuretic hormone secretion[5].

The diagnosis of renal SCC relies mainly on histopathological and immunohistochemical findings[9]. Renal SCC is easily misdiagnosed as other small cell tumours, such as undifferentiated carcinoma, Ewing’s sarcoma, embryonal rhabdomyosarcoma, lymphoma, and primitive neuroectodermal tumour[4]. Immunohistochemical staining and electron microscopic examinations are helpful for the identification. Besides, in the diagnosis of renal SCC, metastatic SCC, especially those originating from the lung, should be excluded[10]. The diagnosis of renal SCC must be based on the patient's clinical history and chest imaging findings. If the patient has a history of pulmonary SCC or the chest imaging examination shows lung neoplastic lesions, renal metastasis of pulmonary SCC should be considered first; however, if urothelial carcinoma is mixed with SCC, the diagnosis of primary renal SCC should be supported[11].

Histologically, renal SCC is similar to other types of SCC and is mostly mixed with other types, including urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma[12]. Under a light microscope, the tumour tissue shows a solid flake or nest-like arrangement with extensive necrosis. The tumour cells are small, similar to lymphocytes, with rare cytoplasm, deep nuclear staining, unclear nucleoli, and frequent mitotic figures[4]. Immunohistochemistry can express specific neuroendocrine markers such as NSE, CD56, Syn, and CgA[13]. Among them, the Ki-67 score seems a better predictor of survival than the degree of differentiation[14]. Serum NSE levels are potentially useful in early diagnosis and treatment monitoring during chemotherapy[15], neural cell adhesion molecule (NCAM or CD56) is the most sensitive neuroendocrine marker, and chromogranin A, a protein found in neurosecretory granules, is the most specific marker[16].

Owing to the small number of primary renal SCC cases, standard treatment guidelines are lacking. Surgery and chemotherapy are currently the most widely used treatment options. Studies have found that targeted drug therapy combined with radical surgery has significant survival benefits compared to simple radical surgery, while radiotherapy is mostly used for postoperative residual lesions or distant metastases[4]. The targeted drug sunitinib is recommended for the treatment of advanced non-clear cell carcinoma[17]. The Department of Urology, Beijing Friendship Hospital Affiliated to Capital Medical University, diagnosed and treated one patient with renal cell carcinoma. The lymph nodes were fused, and the disease entered partial remission 3 mo after sunitinib treatment at 1 mo after surgery; the disease then progressed at 13 mo and the patient died of tumour metastasis after 24 mo. Patient survival was significantly prolonged after surgical resection of the affected kidney and postoperative adjuvant targeted therapy[18]. Although this patient benefited from targeted therapy, the maintenance time was short, and the late-stage treatment effect of this type of tumour requires verification in a large sample of cases.

Some scholars have proposed that simple chemotherapy has a better prognosis than surgery combined with chemotherapy, suggesting that chemotherapy should be the first choice and surgery should only be used to treat local symptoms[19]. Other scholars have proposed that, for patients whose tumours are confined to the kidney, early surgical treatment can enable long-term survival, and the prognosis of patients with clinical stage pT1-pT2 is significantly better than that of patients with pT3-pT4 disease, with a median survival time of 31 and 8 mo, respectively[20]. In a study of 14 cases of renal SCC, Si *et al*[21] found that one patient with SCC limited to the kidney survived tumour-free after surgery for 137 mo. However, a recent study reported no significant difference in estimated median survival across individual treatment modalities. Multimodal therapies likely merit particular investigative attention in terms of growing evidence supporting their use in treating other primary small cell malignancies of the genitourinary tract[22].

In this case, the patient's condition changed rapidly and distant metastasis occurred within 1 year. When the disease was diagnosed, the patient was already in the late stage and had missed the opportunity for early radiotherapy and chemotherapy. It is difficult to obtain suitable specimens for relevant pathological examinations without surgery, such as when the patient's urine exfoliated cells are negative. In addition, some studies reported that the early application of platinum-based chemotherapy can improve the survival rate, and patients who received platinum-based regimens had a median survival of 20 mo *vs* 8 mo for those who received other regimens[23]. Our patient showed an improving trend with the platinum-based chemotherapy regimen. Patrick also reported an 80-mo survival of a patient who underwent nephroureterectomy plus multiple metastasectomies followed by chemotherapy with octreotide, temozolomide, and capecitabine[13]. This is the first report of the use of a somatostatin analogue in the management of primary upper urinary tract SCC. Having no fairly large series capable of allowing a randomized study, their approach requires confirmation in broader studies. Neoadjuvant chemotherapy may also be effective at reducing the pathological stages of SCC[8,24]. However, these treatments are insufficient to achieve a cure, and other strategies are needed to improve the treatment of this deadly cancer. SCRC-1 was the first cell line derived from renal SCC[25]. However, based on this cell line and its related characteristics, further studies of the immunobiology and histogenesis of this rare malignant disease are lacking. These tumours are reportedly involved in c-kit expression and platelet-derived growth factor receptor-α (PDGFRA) mutations[26], which may be potential therapeutic targets[2]; drugs targeting c-kit and/or PDGFRA may be promising topics of future research[12]. In summary, new molecular therapies and immunotherapies for these tumours are still under active exploration and research.

The reason why our patient developed the disease so rapidly is related to the fact that it was diagnosed very late. Interestingly, the patient also underwent surgery in 2019 and did not have the disease, indicating that the tumour was highly malignant. In previous studies, renal SCC had a poor prognosis with a median overall survival, and 95% confidence interval of 9.9 mo (range, 6.9-31.6 mo), and more patients died of tumour metastasis in the short term, mostly from lung, brain, liver, and other systemic metastases. Early detection of the tumour, use of cisplatin-based chemotherapy, and careful follow-up for local recurrence or frequent metastasis within 6 mo after the primary treatment could be important for improving overall survival[27].

**CONCLUSION**

In conclusion, primary renal SCC is an extremely rare tumour for which neuroendocrine markers are helpful for making its pathological diagnosis. Limited available data indicate that the disease has an aggressive natural history and poor prognosis. Clinical stage, tumour composition, and sex may be important factors in determining prognosis. Close follow-up within 6 mo after the initial treatment is the key to an improved overall survival, and once metastases occur, the survival time is substantially reduced. We suggest a comprehensive treatment approach, which currently involves the combination of surgery and chemotherapy, but clinical experience is limited and more data are needed to determine its optimal treatment.

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**Footnotes**

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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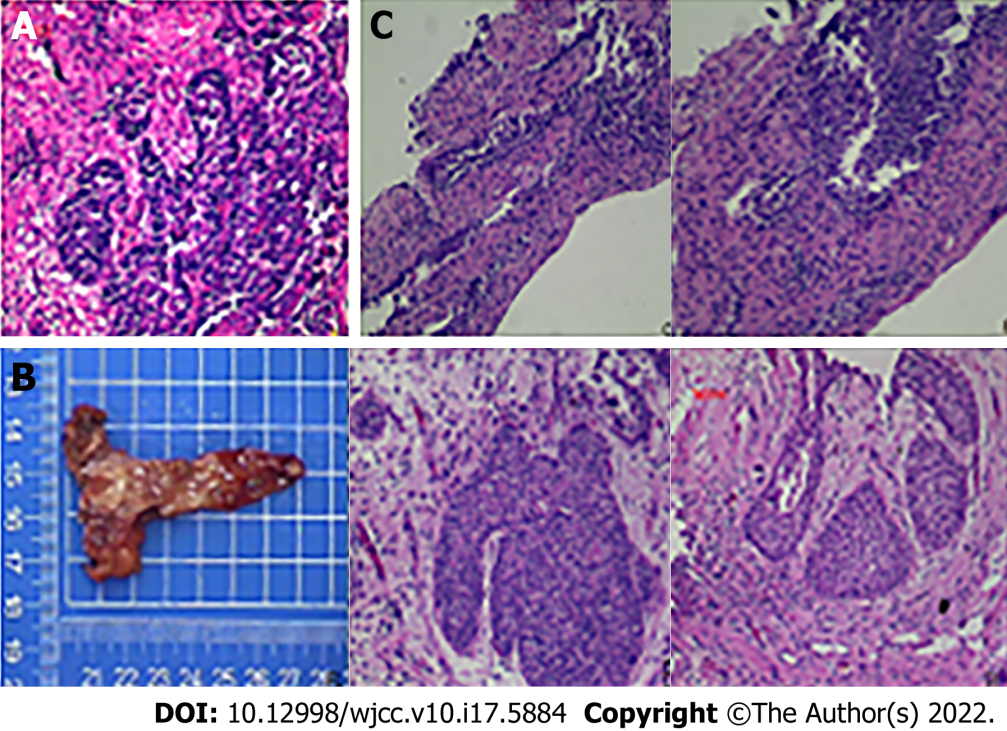
Grade C (Good): C

Grade D (Fair): 0

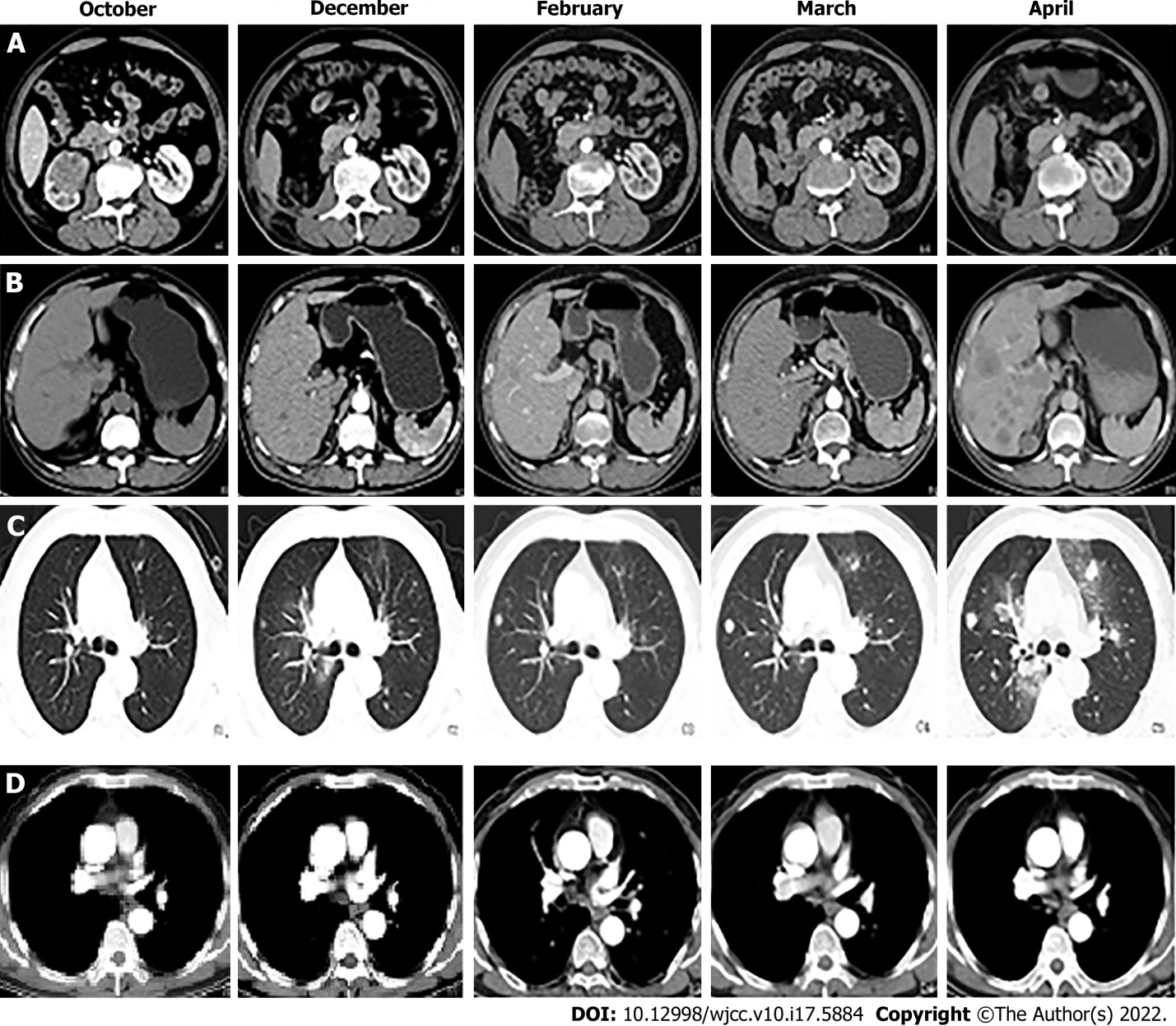
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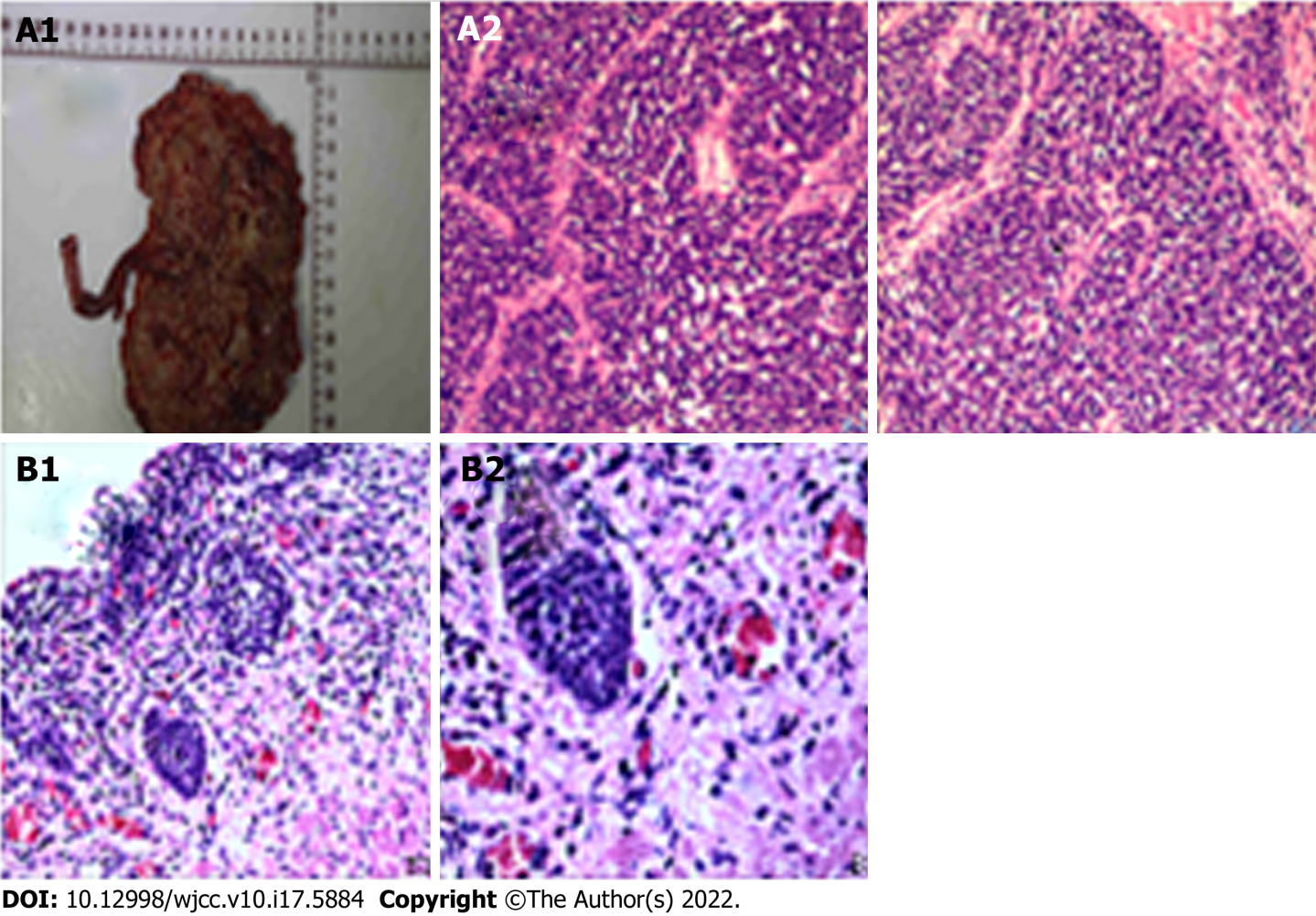
**Figure Legends**



**Figure 1 Postoperative pathology in 2016 and 2019.** A: After ureteral biopsy in 2016. Carcinoma tissue was suspected. Under the microscope, mucosal tissue was mixed with hemorrhagic necrotic tissue, and the surface of the mucosa was covered with urothelium, which showed papillary or solid nest like inverted growth. The tumor nucleus was oval, the cytoplasm was deep, mitosis was occasionally seen, and the focal area seemed to be a staggered arrangement of solid nestlike cells and proliferative stroma; B: After ureteral bladder replantation. Chronic mucositis and mild atypical hyperplasia was considered. Under the microscope, the urinary tract epithelium covered by the mucosal surface of some areas proliferated, and grew to the lamina propria to form a small nest or glandular tube-like structure, focal squamous metaplasia, partial mucosal surface necrosis, covered with a large amount of red staining without structure, and significant interstitial edema in the lamina propria; C: after ureteral biopsy in 2019. Polypoid change was showed. Under the microscope, part of the surface is lined with hyperplastic urothelial epithelium and lamina propria fibrous interstitial hyperplasia.



**Figure 2 There are the results of computed tomography examination before and after operation.** There was no obvious occupation of liver, lung and mediastinum before operation, but these sites began to occupy space since December, especially the change was quite rapid between March and April, and tumor metastasis occurred at the operation site. A: Kidney; B: Liver; C: Lung; D: Mediastinum.



**Figure 3 Postoperative pathology in 2020.** High-grade invasive papillary urothelial carcinoma and small cell carcinoma were suspected. A: Under the microscope, tumor cells were composed of two components: one type of cells was nest-like arrangement, with larger cell volume, abundant cytoplasm, large nuclei, deep staining and obvious atypia; the other type of cells was uniformly distributed in sheets, with medium to small cells, abundant cytoplasm or medium cytoplasm, and round nuclei. And the boundary between the two forms is clear (A1 and A2); B: There was no obvious abnormality at the broken end of the ureter (B1 and B2).

**Table 1 Ninety-two globally published cases of renal small cell carcinoma from 1984 to 2022 and their clinical characteristics and treatment options**

|  |  |  |
| --- | --- | --- |
| **Features** | **Classifications** | **Cases (%)** |
| Age (yr) | ≤ 55 | 38 (41.3) |
|  | > 55 | 54 (58.7) |
| Gender | Male | 50 (54.3) |
|  | Female | 42 (45.7) |
| Clinical presentation | Flank/abdominal pain | 55 (60.0) |
|  | Hematuria | 32 (34.7) |
|  | Lump | 11 (11.9) |
|  | Neurological symptoms | 5 (5.4) |
|  | Other nonspecific symptoms | 7 (7.6) |
| Size (cm) | ≤ 10 | 43 (58.9) |
|  | > 10 | 30 (41.1) |
| Affected side | Right | 40 (48.1) |
|  | Left | 43 (51.9) |
| pT stage | T1-T2 | 24 (27.6) |
|  | T3-T4 | 63 (72.4) |
| Renal vein tumor thrombus | Yes | 16 (34.8) |
|  | No | 30 (65.2) |
| Lymph node metastasis | Yes | 41 (50.0) |
|  | No | 39 (50.0) |
| Distant metastasis | Yes | 23 (28.3) |
|  | No | 58 (71.7) |
| Surgery | Yes | 74 (81.3) |
|  | No | 17 (19.8) |
| Chemotherapy | Yes | 51 (68.0) |
|  | No | 24 (32.0) |
|  | Cisplatin | 29 (56.9) |
|  | Other | 22 (43.1) |



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