

## CASE REPORT

# Primary Small-Cell Neuroendocrine Carcinoma of the Kidney with Urothelial Carcinoma: A Case Series and Literature Review

Runlin Feng<sup>1†</sup>, Yanping Tao<sup>2†</sup>, Wen Zhang<sup>3†</sup>, Jihong Deng<sup>3\*</sup>, Shuangyue Liu<sup>3\*</sup>

<sup>1</sup>Department of Pathology, The Second Affiliated Hospital of Kunming Medical University, Kunming 650101, Yunnan, China

<sup>2</sup>Department of Emergency, Kunming Third People's Hospital, Kunming Medical University, Kunming, 650000, Yunnan, China

<sup>3</sup>Department of Gynecology, Kunming Maternity and Child Care Hospital, Kunming, 650000, Yunnan, China

<sup>†</sup>These authors contributed equally to this work

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### \*CORRESPONDING AUTHORS

Shuangyue Liu

E-mail: liushuangyue320@126.com

Jihong Deng

E-mail: jihongdeng@126.com

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**Abstract:** Primary small-cell neuroendocrine carcinoma of the kidney with urothelial carcinoma is very rare, and it has a unique pathomorphology and immunohistochemical phenotype. Since it is easily missed diagnosed or misdiagnosed, it needs to be differentiated from a variety of other tumors. In addition to poor prognosis, the carcinoma also has strong invasive ability. The clinicopathological characteristics, immunohistochemical phenotype, and diagnosis and differential diagnosis of four patients with primary small-cell neuroendocrine carcinoma with urothelial carcinoma were retrospectively analyzed, and the relevant literature was reviewed. Three cases occurred in the left kidney and one case occurred in the right kidney. The main clinical symptoms were gross hematuria and waist pain. Tumor histological morphology and immunohistochemical markers support small-cell neuroendocrine carcinoma with urothelial carcinoma.

**Keywords:** Renal neoplasms, Small-cell neuroendocrine carcinoma, Urothelial carcinoma, Clinicopathological features, Immunohistochemical phenotype

## 1. Introduction

Primary neuroendocrine tumors of the urinary system are very rare in the clinical setting. In the fourth edition of the World Health Organization (WHO) classification of kidney tumors, neuroendocrine tumors are divided into well-differentiated neuroendocrine tumors, small-cell neuroendocrine carcinomas, large cell neuroendocrine carcinomas, paraganglioma, and pheochromocytoma. The more common ones are well-differentiated neuroendocrine tumors and small-cell neuroendocrine carcinomas. However, the reports about small-cell neuroendocrine carcinoma combined with high-grade urothelial carcinoma are very rare, and only two cases have been reported<sup>[1,2]</sup>. Here, we reported four cases of primary small-cell neuroendocrine carcinoma of the kidney with urothelial carcinoma and presented the related literature, aiming to improve the level of awareness of the disease.

## 2. Case presentation

### 2.1. Patients

Four cases of primary small-cell neuroendocrine carcinoma of the kidney with urothelial carcinoma were confirmed by the pathologist in the Second Affiliated Hospital of Kunming Medical University from 2015 to 2020. The clinical history, imaging data, and follow-up of the patient's condition were collected and sorted, and the specimens removed during the operation were collected and sorted. The specimens were subject to incision, fixation with 4% neutral formaldehyde for 12 h, paraffin embedding, sectioning, hematoxylin and eosin staining, and immunohistochemical detection, and the interpretation was performed under a microscope. Informed consent of the four patients was obtained, and the study was approved by the medical ethics committee of the hospital to ensure that the rights and safety of the subjects are protected.

### 2.2. Clinical data

Among the four patients, there were two males and two females. The average age of onset was 49 years (age range: 38–57 years). The tumor was found in the left kidney in three cases and in the right kidney in one case. The maximum diameter of the tumor was 4.3–7 cm. The main clinical symptoms were gross hematuria and waist pain (**Table 1**). All four patients underwent radical nephrectomy. After the operation, the specimen tissues were sent for examination and incision. The cut surface was grayish-white, grayish-red, and tough, and the margin of the surrounding normal kidney tissue was clear. Three cases had lesions necrosis, two cases had bleeding, and one case had cystic degeneration.

### 2.3. Pathological characteristics

Under the microscope, the tumors were composed of two components (**Figure 1**). Most (about 65–80%) of the tumors were composed of small round cells with uniform morphology and poor differentiation. Most of them were lymphocyte-like or oat cells. Their nuclei were finely granular, with inconspicuous nucleoli and increased mitotic figures. Its cytoplasm was sparsely basophilic or naked, with diffuse tumor cells and extensive necrosis. A small part (approximately 20–35%) of tumors was composed of papillary structures. The polar orientation, nuclear size, morphology, and chromatin structure of the papillary structures of some cells had mild atypia, and mitotic figures were rare. Usually confined to the lower half of the urothelium, it is a low-grade nuclear area, while some papillary structures and cells had obvious atypia, structurally, the cells were irregularly arranged. The cell pleomorphism ranges from moderate to obvious, and the nuclear chromatin was clumped. Nucleoli were prominent and irregular, and mitotic figures were more common, and they were high-level nuclear regions.

### 2.4. Immunohistochemical phenotype

The immunohistochemical expressions of the two tumor components are different (**Table 2** and **Figure 2**). The immunohistochemistry of the small-cell patch area with the same shape showed positive neuroendocrine markers such as chromogranin A (CgA), synaptophysin (Syn), and cell adhesion molecule (CD56), while the urothelial markers were negative, and Ki67 was positive. The rate of positive detection was 40%. The neuroendocrine markers in the papillary region were negative, while the urothelial markers GATA3, CK7, CK20, carcinoembryonic antigen (CEA), and uroplakin III were positive. In the low-grade nuclear region, CK7 was weakly positive, CK20 and CEA were both negative, and the Ki67-positive rate was only

**Table 1.** Clinicopathological characteristics of four cases of primary small-cell carcinoma of kidney with urothelial carcinoma

Patient gender/age at diagnosis (years)	Clinical symptoms	Location of tumor	Tumor diameter (cm)	Lymph node metastasis	Tumor components and proportion	Follow-up time (months)	Prognosis
M/55	Back pain	Lower pole of the left kidney	5.5	Yes	Small cells (80%) and low-grade papillary (20%)	16	Bad
M/49	Hematuria	Upper pole of the left kidney	7	No	Small cells (70%) and low-grade papillary (30%)	21	Good
F/38	Hematuria	Upper pole of the right kidney	4.3	No	Small cells (65%) and high-grade papillary (35%)	26	Good
F/57	Hematuria	Upper pole of the left kidney	5	Yes	Small cells (70%) and high-grade papillary (30%)	13	Good

5%; while in high-grade nuclear areas, the expression of CK7, CK20, and CEA was strong, and the Ki67-positive rate reached 20%.

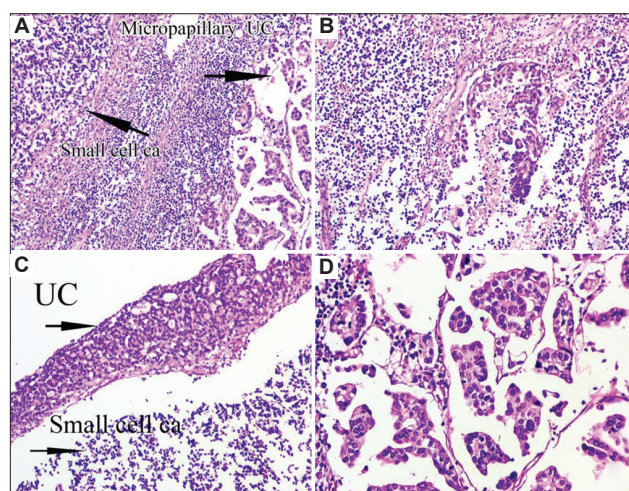
### 2.5. Final diagnosis and follow-up

In these of four cases, two cases were diagnosed as small-cell neuroendocrine carcinoma with high-grade urothelial carcinoma, and two cases were diagnosed as small-cell neuroendocrine carcinoma with low-grade urothelial carcinoma. None of the four patients received chemotherapy, immunotherapy, or other related treatments. Follow-up that lasted for 13–26 months, with an average of 19 months, was performed after operation. Until November 2020, three patients had a good prognosis and one patient had recurrence.

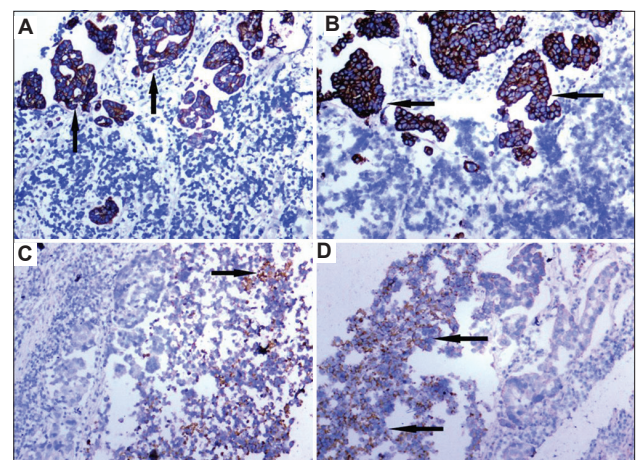
### 3. Discussion

Primary renal neuroendocrine tumors are very rare tumors, accounting for <1% of renal epithelial tumors<sup>[3]</sup>, with unique neuroendocrine tumor morphology and immunophenotype, which can occur in the renal pelvis or renal parenchyma. It can exist alone or coexist with other types of tumors, such as squamous cell carcinoma, adenocarcinoma, and urothelial carcinoma<sup>[4,5]</sup>. Despite that coexistence of these tumors has rarely been reported, in this case series, we reported four cases with this condition. Small-cell neuroendocrine carcinoma is a subtype of neuroendocrine carcinoma. The most common type of renal neuroendocrine tumors is carcinoid<sup>[6]</sup>, followed by

small-cell neuroendocrine carcinoma<sup>[7,8]</sup>. Of more than 50,000 cases of extrapulmonary small-cell neuroendocrine carcinoma reported in the United States from 1992 to 2010, there were only more than 30 cases that have originated in the kidney and renal pelvis<sup>[9]</sup>. This indicates that the incidence of small-cell neuroendocrine cancer that occurs in the kidney is very rare. Small-cell neuroendocrine carcinomas that occur in the renal parenchyma usually occur alone, while the small-cell neuroendocrine carcinomas that occur in the renal pelvis mostly coexist with non-neuroendocrine carcinomas. However, in reality, due to the large size of the tumor, it is generally difficult to distinguish whether the tumor is derived from the renal parenchyma or renal pelvis. The careful observation of the specimens of the four cases under the microscope revealed the presence small-cell neuroendocrine carcinoma and urothelial carcinoma, so it is speculated that the tumor may originate from the renal pelvis. As for the mechanism of small-cell neuroendocrine carcinoma combined with urothelial carcinoma, currently, it is subject to academic controversies. Most scholars believe that the pluripotent stem cells in the urothelium can induce malignant differentiation of small-cell carcinoma and non-small-cell carcinoma under the action of certain tumorigenic factors. This explains why the mechanism of small-cell neuroendocrine carcinoma is often associated with urothelial carcinoma<sup>[10]</sup>. Some scholars also believe that renal small-cell neuroendocrine carcinomas mostly invade the renal pelvis and coexist *in situ* with papillary



**Figure 1.** (A) The tumor is composed of two components: Small-cell carcinoma and urothelial carcinoma components (hematoxylin and eosin [HE] staining;  $\times 40$ ). (B) The ratio of small-cell carcinoma and urothelial carcinoma is about 4:1 (HE staining;  $\times 40$ ). (C) The upper part is a low-grade urothelial carcinoma component, and the lower part is a poorly differentiated small-cell carcinoma component (HE staining;  $\times 100$ ). (D) Urothelial carcinoma with nipple structure, slender nipple, some mild fusion, irregularly enlarged nucleus, and inconspicuous nucleoli (HE staining;  $\times 200$ ).



**Figure 2.** (A) Positive expression of CK20 in urothelial carcinoma (shown by the arrow), but not in small-cell carcinoma (SP;  $\times 100$ ). (B) Positive expression of CK7 in urothelial carcinoma (shown by the arrow), but not in small-cell carcinoma (SP;  $\times 100$ ). (C) Positive expression of Syn in small-cell carcinoma (shown by the arrow), but not in urothelial carcinoma (SP;  $\times 100$ ). (D) Positive expression of CgA in small-cell carcinoma (shown by the arrow), but not in urothelial carcinoma (SP;  $\times 100$ ). The SP detection kit was designed based on the principle that there is a strong affinity between biotin and streptomycin antibiotic protein. The secondary antibody is labeled with biotin and can be linked to the labeled peroxidase *Streptomyces* antibiotic protein.



**Table 2.** Immunohistochemistry of four cases of renal primary small-cell neuroendocrine carcinoma with urothelial carcinoma

Case	Tumor component	CK7	CK20	CEA	SyN	CgA	CD56	Ki67	GATA3	Uroplakin III
1	Small cell	-	-	-	+	-	+	50%	-	-
	Papillary structure	+	-	-	-	-	-	5%	+	+
2	Small cell	-	-	-	+	-	+	45%	-	-
	Papillary structure	+	-	-	-	-	-	5%	+	+
3	Small cell	-	-	-	+	+	+	40%	-	-
	Papillary structure	+	+	+	-	-	-	25%	+	+
4	Small cell	-	-	-	+	-	+	35%	-	-
	Papillary structure	+	+	+	-	-	-	15%	+	+

urothelial carcinomas, suggesting that small-cell neuroendocrine carcinoma may originate from pluripotent stem cells with multidifferentiation potential in the renal pelvic mucosa<sup>[11]</sup>.

Small-cell neuroendocrine carcinoma combined with urothelial carcinoma is more common in adults, and there is no clear gender difference. The clinical manifestations are similar to those of other kidney tumors. Most of them are triad of low back pain, abdominal masses, and hematuria. A small number of patients have bladder irritation such as frequent urination, urgency, and dysuria. Their systemic symptoms mainly include anorexia and weight loss, but neuroendocrine symptoms have never been reported. The imaging features of small-cell neuroendocrine carcinoma combined with urothelial carcinoma were not significantly different from other renal tumors. On computed tomography (CT), it may show a small amount of blood vessels or almost no blood vessels or show a small amount of uneven enhancement or calcification. Pre-operative pathological biopsy can be used to determine the nature and type of the tumor. Whether small-cell neuroendocrine carcinoma is accompanied by urothelial carcinoma and how much urothelial carcinoma accounts for in small-cell neuroendocrine carcinoma requires radical nephrectomy and comprehensive judgment after taking samples from multiple sections and multiple sites. The tumor is usually large in size, with an average diameter of about 7.1 cm. The cut surface is gray and red, and some areas can be necrotic. The morphology of most areas under the microscope is relatively uniform. The cells are mostly lymphocyte-like or oat cell-shaped small cells that are round or oval, and the cytoplasm is sparsely basophilic or naked, and a small part of the area is a papillary urothelial structure of low-grade nucleus and/or high-grade nucleus. Immunohistochemistry often expresses neuroendocrine markers such as CgA,

Syn, NSE, CD56, NF, and CD57 in the small-cell area. However, epithelial markers such as GATA3, CK7, CK20, and CEA are often expressed in the papillary urinary tract. Therefore, the use of neuroendocrine markers, epithelial markers, and renal-derived markers testing should be used together in the diagnosis of this tumor. Ki67 is mainly used to determine the proliferation activity of cells. The level of Ki67 expression is closely related to the degree of differentiation, invasion, metastasis, and prognosis of the tumor. Given that the expression of Ki67 of small-cell neuroendocrine carcinoma is much higher than that of urothelial carcinoma, it is associated with higher risk of invasion and metastasis as well as worse prognosis.

Small-cell neuroendocrine carcinoma combined with urothelial carcinoma is mostly composed of small cells, while the shape of small-cell neuroendocrine carcinoma might resemble to that of other tumors, so it needs to be differentiated:

- Primitive neuroectodermal tumor: The tumor cells are small but uniform in size. The cells are usually smaller than three lymphocytes. It is composed of round cells, often seen in Homer Wright rosettes, with fine chromatin, small nucleoli, and increased mitotic figures. Immunohistochemistry test shows mostly diffuse expression of vimentin, CD99, and CD117.
- Lymphoma: The cell morphology of lymphoma is very similar to that of small-cell neuroendocrine carcinoma, but the immunohistochemistry test reveals the expression of lymphoid hematopoietic markers instead of neuroendocrine markers.
- Wilms tumor: The incidence of this tumor is mostly concentrated in infants and young children, while small-cell neuroendocrine carcinomas mostly occur in adults. In addition, Wilms tumor is composed of a large number of chrysanthemum-shaped structures,

primitive or naïve epithelioid. It is composed of cells, embryo structure, and immature mesenchymal cells and does not express neuroendocrine markers.

- iv. Small-cell malignant melanoma: Both tumors are small-cell malignant tumors, but small-cell malignant melanoma generally expresses melanocyte markers but not neuroendocrine markers.

#### 4. Conclusions

Renal small-cell neuroendocrine carcinoma combined with urothelial carcinoma is one of the very rare tumors in the urinary system. It is highly aggressive and difficult to be diagnosed by ultrasound, CT, and magnetic resonance imaging before surgery. The diagnosis mainly depends on pathological morphology and immunohistochemical labeling. The prognosis of the patient is related to the size of the tumor, the proportion of small-cell neuroendocrine carcinoma, the degree of tissue invasion, clinical stage, and lymph node metastasis. There is still no standard and effective treatment plan, but radical surgery is the most effective way to prevent tumor recurrence or distant metastasis.

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#### Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

#### Author contributions

R.F. and Y.T. contributed to the conception of the study. W.Z. integrated all information and wrote the manuscript. J.D., S.L., and R.F. provided critical guidance throughout the writing process. R.F., Y.T., J.D., and S.L. compiled information and revised the manuscript. All authors read and approved the final manuscript.

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