Primary small cell neuroendocrine carcinoma combined with squamous carcinoma of the ureter after renal transplantation: a rare case report

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Abstract: A 47-year-old female presented with a 1-month history of painless gross hematuria after undergoing kidney transplant 4 years. Computed tomography revealed mass-like soft tissue density in the middle-lower portion of the right autologous ureter, which was up to the upper margin of the fourth lumbar vertebra, down to the distal ureter near the entrance of the bladder. The patient underwent right autologous nephroureterectomy resection. Gross examination showed a white, partly yellow mass in the middle-lower portion of ureter. Light microscopy showed a small cell neuroendocrine carcinoma (SCNEC) admixed with squamous carcinoma, invading the ureter wall to periureteric fat tissue, and there was invasion of the lymphatic and renal portal vein. The SCNEC was diffusely positive for CD56 and syn, and squamous carcinoma was positive for P40, P63 and CK5/6. Ureteral SCNEC is a rare malignant tumor with high invasiveness and poor prognosis. Diagnosis mainly depends on pathologic morphology and immunohistochemical markers. Positive neuroendocrine markers are one of the important references for this tumor. Surgical treatment and postoperative radiotherapy and chemotherapy are the main treatments according to cases reported.

Keywords: Small cell neuroendocrine carcinoma, squamous carcinoma, ureter, renal transplantation

Introduction

Extrapulmonary small-cell carcinoma (ESCC) is a rare neoplasm, with genitourinary ESCC being second in incidence only to gastrointestinal ESCC [1]. Primary small cell neuroendocrine carcinoma (SCNEC) of the urinary tract is a rare cancer, accounting for less than 0.5% of urinary tract tumors, mostly localized in the bladder and prostate, while its localization in the ureter is rare and has been described in about 40 patients [2] so far. SCNEC of the ureter is an extremely rare condition characterized by aggressive behavior [3].

We describe the clinical characteristics, pathological features and immunohistochemical findings of a primary malignant SCNEC combined with squamous cell carcinoma of the ureter.

Case report

A 47-year-old female presented with painless gross hematuria for 1 month. Her serum creatinine concentration was elevated, a urinalysis showed many red blood cells. Urine cytology test results were negative for several times. She had undergone kidney transplant 4 years ago because of atrophy of her both kidneys. She did not complain of voiding symptoms, such as frequency, hesitancy or dysuria, and had no smoking history.

Imaging features

Abdominal Computed tomography (CT) scan showed three kidneys in the abdominal cavity including two native kidneys and one transplanted kidney. The transplanted kidney was located in the right iliac fossa, and the morphology, size and density were normal. Bilateral autologous kidneys were atrophied and cortices were thinning. The right autologous ureter was enlarged with a mass-like soft tissue density in the middle-lower portion of the right ureter (Figure 1A) (Upper and lower diameter ×
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Left and right diameter × Anteroposterior diameter: 150 mm × 57 mm × 39 mm), which was up to the upper margin of the fourth lumbar vertebra, down to the distal ureter near the entrance of the bladder. The upper ureter of the lesion was slightly dilated, and the right renal pelvis was markedly dilated with hydronephrosis. CT sign: ureteral masses, considering malignancy. Metastatic lesions could be found in peripheral lymph nodes (Figure 1B). A nephroureterectomy was carried out.

Gross examination of the resected specimen showed a segment of ureter 8 cm away from the right renal hilum that had irregular thickening and was nearly solid (Figure 1C), which caused obstruction of the ureter lumen. The mucosa of thickened ureter was smooth with no ulcer lesions and protuberant exogenous mass (Figure 1C). The renal section is multilocular cystic because of renal cortex thinning markedly, hydronephrosis, and ureter ectasia (Figure 1C).

Microscopic examination and immunohistochemical results

Microscopically, the tumor was composed of two morphologic tumor cells. The majority of tumor cells were small round cells, containing finely granular, hyperchromatic nuclei, inconspicuous nucleoli and scanty cytoplasm with a high nuclear:cytoplasmic ratio, and the mitotic count was high. Immunohistochemically, the small round tumor cells were partly positive for urothelial markers (GATA-3), positive for epithelial markers (CK, CK7 and E-cadherin), diffusely positive for neuroendocrine markers (Syn, CD56, focally PGP-9.5 and CgA), and the proliferative index counted by Ki-67 was more than 80% (Figure 2); the tumor was negative for vimentin, TTF-1 and LCA. The component of

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**Figure 1.** CT and gross images of the mass. A. The sagittal view demonstrates that the tumor in the middle and lower segment of the ureter was close to the right transplanted kidney, but not invaded. B. Coronal view shows the right middle and lower segment of the ureter and the adjacent metastatic lymph nodes, and the right upper segment of the ureter and hydronephrosis dilatation of pelvic obstruction. C. Cut section of excised tumor showing the mucosa of thickened ureter (red thick arrow) was smooth with no ulcer lesions and a protuberant exogenous mass (black thin arrow). The renal section is multilocular cystic (black thick arrow).
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In focal regions of the tumor, the other morphologic tumor cells scattered in nests among the above small cells could be observed. These tumor cells were large in size, with abundant cytoplasm, vacuolar nuclei, small distinct nucleoli and the mitotic figures were easily found. These tumor cells were immunohistochemically partly positive for urothelial markers (GATA-3), diffusely positive for CK and markers of squamous cell differentiation (including P40, P63 and CK5/6), and were negative for neuroendocrine markers. The component of the large tumor cells was diagnosed as squamous carcinoma (Figure 2).

**Diagnosis**

In conclusion, a final pathological diagnosis was made as SCNEC (90%) admixed with squamous carcinoma (10%), infiltrating the ureter wall to periureteric fat tissue, and there was invasion of the lymphatic and renal portal vein.
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There was no histologic evidence of metastasis of lymph nodes, because no suspected lymph nodes were removed.

**Discussion**

Genitourinary SCNEC have been reported at many sites, including the renal pelvis [4], urinary bladder [5], urethra, and prostate [6], with extremely rare sites being the ureter as summarized in Fabiola Farci’s report [2]. In total, 41 patients of primary ureteral SCNEC are found in English literature (including our case), and 56.10% (23 of 41) presented painless gross hematuria. Primary ureteral SCNEC is common in middle-aged and elderly people (50~84 years old), and has a preponderance of men, 60.98% (25 of 41) than in women 36.59% (15 of 41) and 1 was not mentioned. 56.10% (23 of 41) was of single histological type of SCNEC, and 43.90% (18 of 41) had one or more associated histotypes, including squamous carcinoma, urothelial carcinoma, lymphoma and sarcoma. Urothelial carcinoma is the most common histologic type combined with SCNEC, accounting for 36.59% (15 of 41) of all cases. The second is squamous cell carcinoma, which accounts for 9.8% (4 of 41). Other, rarer cell types include 1 case of lymphoma and sarcoma, respectively.

Spontaneous small cell carcinoma of the ureter after kidney transplantation is even rarer. The incidence of tumors after renal transplantation was reported to be as high as 7% abroad [7], while only 2.95% in China [8]. There are three main origins of tumor after renal transplantation: (1) Primary malignant tumors in patients after renal transplantation; (2) The recurrence of malignant tumors that already existed before kidney transplantation; (3) Malignant tumors from donor kidneys. A large number of clinical studies and case analysis believe that the main causes leading to primary tumors after renal transplantation include: chronic viral infection (for example: BK virus), low immune function of...
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...the body, genetic susceptibility, advanced age, etc., among which chronic viral infection and immunosuppressive factors are particularly important. In foreign countries, skin cancer and post-transplantation lymphatic tissue proliferative disease (PTLD) are common, while malignant tumors occurring after renal transplantation in China are mainly urinary system tumors after transplantation (55.8%) [8]. Our patient underwent kidney transplant 4 years ago. Due to high dose of immunosuppressive agents, the body was in a state of low or impaired immune function, which caused susceptibility to infection with BK virus. BK virus mainly lurks in renal tubular cells and transitional epithelial cells, and can selectively fuse with tumor cells to promote tumor development in some conditions. In order to exclude the possibility that BK virus triggered the tumor, we detected the expression of BK by immunohistochemistry. Both the two tumor cell components were immunohistochemically negative for BK virus. Long-term use of immunosuppressive agents can inhibit the normal immune function and inhibit the immune function of clearing cancer cells. When immune surveillance dysfunction occurs, immune will be tolerant to tumor antigens, thus causing malignant tumors. The relationship between using immunosuppressive agents and ureteral SCNEC needs further investigation.

Primary ureteral small cell carcinoma is relatively rare and is easily misdiagnosed as other small cell malignant tumors, such as poorly differentiated urothelial carcinoma, embryonic rhabdomyosarcoma, lymphoma, and metastatic small cell carcinoma. Immunohistochemical positivity for neuroendocrine markers is helpful for diagnosis of SCNEC.

The histogenesis of the primary ureteral SCNEC remains unclear. SCNEC of the genitourinary system might originate from multipotential epithelial cells in the genitourinary tract or from intrinsic neuroendocrine cells in the normal genitourinary tract derived from the neural crest during embryogenesis. At present, many scholars support the theory of stem cell origin, and believe that primary SCNEC and epithelial carcinoma of urinary tract have the same origin. This is supported by the fact that SCNEC often coexist with other histologic types such as squamous carcinoma, and urothelial carcinoma. Our case presented with SCNEC combined with squamous carcinoma of the ureter, in agreement with the hypothesis that these tumor cells originate from multipotential stem cells of the ureter. Cheng et al. [9] further confirmed that SCNEC and urothelial carcinoma of bladder originated from the same tissue cells at the molecular genetic level. In our case, both SCNEC and squamous carcinoma was immunohistochemically positive for markers of urothelium (GATA-3 and CK7) (not shown), which may also be an evidence of the same origin of SCNEC and squamous carcinoma or different differentiation of urothelium. However, the ureteral SCNEC component was positive for several neuroendocrine markers, in agreement with the hypothesis that SCNEC originates from intrinsic neuroendocrine cells during the embryogenesis. Further evaluation is required to clarify the pathogenesis and origin of ureteral SCNEC.

As with small cell lung cancer (SCLC), smoking might be the primary risk factor for ureteral SCNEC; patients with SCNEC at any site in the urinary tract have been reported to have a history of heavy smoking. In reported cases of ureteral SCNEC, 9 patients had a history of smoking among the 16 patients collected smoking history, which accounts for 56.25%. Most patients had a smoking history for many years [2, 10-15]. Although SCNEC of the genitourinary tract may also occur in nonsmokers as our patient, we also believe that smoking is the main risk factor for the development of ureteral SCNEC. Further clarification of the mechanism and relationship between smoking and ureteral SCNEC is required.

Because of the rarity of ureteral SCNEC, standard treatment has not yet been established. Multimodal therapy, including surgery, radiation and chemotherapy, has been administered previously [1]. This multimodal therapy is based on the histological similarity of SCNEC of the ureter with SCLC. However, Ismaili [5] does not agree that the treatment should be analogous to that used in the treatment of SCLC. Rather, therapy should be guided by the anatomic site of the disease. Ahsaini successfully managed small cell neuroendocrine carcinoma of the urinary tract with neoadjuvant chemotherapy [14]. Osaka reported a case of ureteral invasive SCNEC successfully treated by neoadjuvant chemotherapy and laparoscopic nephroureterectomy [10]. Effective therapeutic modalities and treatment protocols for ureteral SCNEC need to be further evaluated. Most primary ureteral SCNEC tend to progress rapidly, with most...
dying of disease within 1 year. Our patient did not receive chemotherapy according to the doctor’s advice and survived 5 months after discharge.

Conclusion

We report a rare case of primary SCNEC combined with squamous carcinoma in the ureter. Primary ureteral small cell carcinoma is very rare, and primary small cell carcinoma after kidney transplantation is even more rarely reported. The tumor has a high degree of malignancy and high mortality. After excluding metastasis, primary diagnosis is made. The pathogenic factors may be related to the long-term application of immunosuppressants. Urologists and pathologists should be aware of the possibility of SCNEC in the ureter in patients presenting with a ureteral mass or painless gross hematuria. Our report is intended to increase awareness of diagnosis of primary SCNEC after renal transplantation. Further prospective studies and standardized diagnostic criteria are needed to clarify the epidemiology and effective treatment protocol for ureteral SCNEC.

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Disclosure of conflict of interest

None.

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