Neuroendocrine Carcinoma of the Kidney and Bladder with Loss of Heterozygosity and Changes in Chromosome 3 Copy Number

Atsushi Okada
Keitaro Iida
Takashi Hamakawa
Yukihiro Umemoto
Takahiro Yasui
Noriyasu Kawai
Keiichi Tozawa
Shoichi Sasaki
Yutaro Hayashi
Kenjiro Kohri

Corresponding Author: Atsushi Okada, e-mail: a-okada@med.nagoya-cu.ac.jp

Conflict of interest: None declared

Patient: Female, 77
Final Diagnosis: Neuroendocrine carcinoma of the kidney and bladder
Symptoms: Right lumbar pain
Medication: None
Clinical Procedure: CT • needle biopsy of renal tumor • transurethral resection of bladder tumor
Specialty: Urology
Objective: Rare disease
Background: Neuroendocrine carcinomas (NECs) of the urological organs are observed occasionally, although simultaneous development in the kidney and bladder has not been reported.
Case Report: We report a case of a metastatic NEC of the kidney and bladder in a 77-year-old woman who underwent renal biopsy and transurethral resection of the bladder tumor. Pathological examination revealed NEC in the kidney and the bladder samples. Immunohistochemical examination revealed strongly positive staining for synaptophysin, chromogranin A, and CD56, and focally positive staining for cytokeratin AE 1/3 and Cam 5.2. Fluorescence in situ hybridization confirmed the increased chromosome 3 copy number, and loss of hybridization in 3q21, 5q22-23, 10q26, and 13q14 was detected when the tumor samples were compared with normal samples.
Conclusions: This is a rare case of NEC-specific genetic abnormalities in a kidney-derived tumor, and is the first report to identify kidney-derived NEC that metastasized to the bladder via the urinary tract.

MeSH Keywords: Carcinoma, Neuroendocrine • Chromosome Aberrations • Cytogenetic Analysis • Kidney Neoplasms • Loss of Heterozygosity • Urinary Bladder Neoplasms

Abbreviations: NEC – neuroendocrine carcinoma; LDH – lactate dehydrogenase; NSE – neuron-specific enolase; LOH – loss of hybridization

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Background

Neuroendocrine carcinomas (NECs), including small cell carcinomas, are poorly differentiated epithelial neoplasms that exhibit neuroendocrine differentiation and often occur in the mucous membranes of the organs (e.g., bronchi [1] and gastrointestinal tract [2]) where neuroendocrine cells typically reside. The pathological features of NEC are uniform small cells with scant cytoplasm, powdery chromatin, and inconspicuous nucleoli. However, it is rare that NEC arises in the kidney or bladder as a primary lesion, although these tumors often have characteristic immunohistochemical features and genetic/chromosomal alterations that are unique from NECs that arise from respiratory lesions [3–5]. In this case, we experienced a very rare metastatic NEC that spontaneously arose in the kidney and bladder, and we investigated the morphological, immunohistochemical, and genetic backgrounds of this case, considering the available literature.

Case Report

A 77-year-old woman with no other personal or familial medical history presented with a 1-month history of right lumbar pain. Physical examination revealed a tender mass in the deep right hypochondrium. The urinalysis results were unremarkable, with normal soluble IL-2 receptor levels. However, we detected a light inflammatory reaction (C-reactive protein: 3.77 mg/dL), extremely high lactate dehydrogenase (LDH: 1474 IU/L) and neuron-specific enolase (NSE: 1600 ng/mL, normal: £16.3 ng/mL), and slightly elevated carcinoembryonic antigen (6.3 mg/mL, normal: £5.0 mg/mL) and carbohydrate antigen 19-9 (39.5 U/mL, normal: £37.0 U/mL) levels. Class V urine cytology was detected, and computed tomography revealed a right renal mass without distinct border in the kidney, which overlapped the para-aorta lymph nodes, with right hydronephrosis and hydroureret and a broad-based non-papillary submucosal tumor (Figure 1), with suspected multiple metastatic lesions on the left infraclavicular lymph node, left humerus, right 4th rib, and right femur. Therefore, needle biopsy of the right renal tumor and transurethral resection of the bladder tumor were performed.

Histological examination of the tumor with hematoxylin and eosin staining revealed a diffuse tumor composed of small round cells with a high nucleus-cytoplasm ratio in both the renal and bladder specimens, and extensive necrosis (Figure 2). In addition, the differentiation tendencies (e.g., ductal formation or cornification) were also evaluated, and immunohistochemistry revealed focal staining of cytokeratins as epithelial markers, as well as strong positive staining for synaptophysin, chromogranin A, and CD56 as neuroendocrine markers (Table 1). Therefore, NEC of the right kidney and bladder was diagnosed. To confirm the diagnosis, transmission electron microscopy was performed (data not shown), and small round cells were observed, which had poor cytoplasm, a high nuclear-cytoplasmic ratio, and high-density endocrine granules (approximately 50–100 nm) in the cytoplasm.

In addition, fluorescence in situ hybridization was used to compare the chromosome 3 copy number using CEP3 probes, and the results indicated 3 signals per nucleus in 58.5% of the tumor cells (Figure 3). To evaluate the loss of heterozygosity (LOH), 12 regions, which has been reported in small cell carcinomas or endocrine tumors [3,8–12], were analyzed using GeneMapper software (Applied Biosystems, Foster City, CA, USA) and 4 loci (D3S1768, D5S346, D10S169, and D13S153).
Figure 2. Pathological findings from the tumor regions of the kidney and bladder. Hematoxylin-eosin staining. Magnification: 20× (A) and 400× (B).

Table 1. Immunohistochemical characteristics of the neuroendocrine carcinoma of the kidney and bladder.

| Antigen            | Renal biopsy | Bladder tumor |
|--------------------|--------------|---------------|
| CK AE1/3           | + Focal      | + Focal       |
| CK Cam5.2          | + Focal      | + Focal       |
| Vimentin           | +            | +             |
| CD3                | –            | –             |
| CD5                | –            | –             |
| CD10               | –            | –             |
| CD20               | –            | –             |
| CD45               | –            | –             |
| CD79a              | –            | –             |
| TdT                | –            | –             |
| Granzyme B         | –            | –             |
| CD56/NCAM          | ++           | ++            |
| Synaptophysin      | +++          | +++           |
| Chromogranin       | +            | + Focal       |
| NSE                | +            | + Focal       |
| TTF-1              | –            | –             |
| S100               | –            | –             |
| SMA                | –            | –             |
| Desmin             | –            | –             |
| Myoglobin          | –            | –             |
| WT-1               | –            | –             |
| CD99/MIC2 protein  | +            | +             |

CK – cytokeratin; CD – cluster of differentiation; TdT – terminal deoxynucleotidyl transferase; NCAM – neural cell adhesion molecule; NSE – neuron-specific enolase; TTF-1 – thyroid transcription factor-1; SMA – smooth muscle actin; WT-1 – Wilms’ tumor protein 1.
For 3q21, 5q22-23, 10q26, and 13q14, respectively) of LOH were determined (Figure 4).

For the initial 2 weeks to perform the renal biopsy, transurethral resection and pathological diagnosis, this case indicated a sudden increase in LDH to 13,060 U/L. Based on the National Comprehensive Cancer Network guidelines, we initiated a combination of carboplatin and etoposide, which was followed by the therapy that was provided for the unresectable NEC. After 2 courses, a decrease in the number of metastatic foci (including in the kidney), NSE (25.1 ng/mL), and LDH (1,366 U/L) was observed. However, the recovery from myelosuppression was undesirable and medication of the zoledronic acid for the exacerbation of hypercalcemia and of the opioid for the cancer pain were induced before the third course, and the patient did not expect further aggressive treatment and moved to a hospital specializing in palliative care. Thereafter, her physical state worsened immediately, and she subsequently died of the cancer the next month.

Discussion

Urinary tract-derived NEC is rarely reported [3–5], and this is the first report of simultaneous NEC in the kidney and bladder.

![Figure 3](image1.png)

**Figure 3.** Fluorescence in situ hybridization using the CEP3 probe to detect chromosome 3 in the tumor region. Arrows indicate CEP3 probe signals, and trisomy of chromosome 3 was detected.

![Figure 4](image2.png)

**Figure 4.** Representative results of detection of loss of hybridization (LOH) in the neuroendocrine carcinoma of the bladder. The 4 loci (D3S1768, D5S346, D10S169, and D13S153 for 3q21, 5q22-23, 10q26, and 13q14, respectively) of LOH were determined. Arrows indicate the alleles that exhibited LOH in the tumor samples.
On the basis of the pathological and genetic characterization, we investigated the origin of the metastatic NEC.

Shurtleff et al. reviewed the characteristics of kidney-derived NEC [6]. Although the pathologic origin of primary renal NEC is unclear, it is thought to be an ancestor cell incorporated into the renal parenchyma during organ formation. Small nests of paraganglion cells in the kidney hilum may be the origin of neuroendocrine tumors [7]. In addition, neuroendocrine differentiation is rarely observed in microcystic urothelial cancer of the renal pelvis. Furthermore, renal NEC from metaplasia of the neuroendocrine cells in the stroma of the renal pelvis mucosal membrane has been reported [6]. In all the reported cases, primary renal NEC was generated in the renal pelvis area, and this condition does not contradict our case.

In contrast, the International Agency for Research Cancer describes bladder NECs as small cell bladder cancers [8], and has commented that almost all urinary tract small cell carcinomas arise in the urinary bladder. Therefore, it is difficult to determine the tumor’s origin morphologically, as bladder NECs cannot be clearly differentiated from renal NECs by using immunohistochemistry. Recently, Neşe [13] et al. reported high expression of somatostatin receptor type 2A (SSTR-2A) in small cell carcinomas of the bladder and that SSTR-2A expression was correlated with survival as a poor prognostic factor. Jiang Y [14] et al. investigated clinicopathological data from 17 NEC of the bladder cases and concluded that immunohistochemical markers such as CD56, Syn, CgA, and CKpan could be helpful in determining the diagnosis and differential diagnosis. However, it is thought that the immunohistochemistry for such markers cannot identify the origin of NECs generated urinary tract (kidney or bladder).

NECs that are generated in the urological organs often have unstable hereditary and genetic variations [4,9,10] in contrast to pulmonary carcinoid tumors. In cytogenetic studies of pulmonary carcinoid tumors, chromosome 3 abnormalities have not been detected [15,16], while abnormal chromosome 3 copy numbers and LOH in 3p are considered characteristic of kidney-derived tumors [3]. However, it has been suggested that a bladder NEC is a tumor with unstable heredity and several typically cytogenetic changes. The most frequently detected changes in bladder NECs are deletions in 10q, 4q, 5q, and 13q, as well as insertions in 8q, 9p, 6p, and 20q. In addition, large amplifications have been observed at 1p22-32, 3q26.3, 8q24 (including c-Myc), and 12q14-21 (including MDM2), which may potentially pinpoint the location of the activated oncopgenes [8,9]. In the present case, LOH was detected at 3q21 (D3S1768, characteristic of kidney NECs) [3], 9q22-q23 (D5S346, characteristic of several urothelial and rectal tumors) [10], 10q26 (D10S1569, characteristic of invasive bladder cancers and thyroidal tumors) [11], and 13q14.2 (D13S153, characteristic of some prostate cancers and skin squamous cell carcinomas) [12].

This is the first reported case of simultaneous occurrence of renal and bladder NECs, and further genetic examination determined that this tumor was a kidney-derived NEC metastasized to the bladder via the uririnary tract.

Conclusions

This is a rare case of neuroendocrine carcinoma with specific genetic abnormalities in a kidney-derived tumor, and is the first report to identify a kidney-derived NEC that metastasized to the bladder via the urinary tract.

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Conflicts of interest

None.

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