

Primary large-cell neuroendocrine carcinoma of the upper ureter

A case report

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Abstract

Rationale: The incidence of primary large-cell neuroendocrine carcinoma (LCNEC) is extremely rare in the urinary tract. In the present study, we investigated a case of primary LCNEC associated with the upper ureter.

Patient concern: A 58-year-old Korean female patient with right ureter mass, which was accidentally detected. An enhancing mass measuring 3.3 cm in size was found in the computed tomography (CT) scan. No definitive evidence of lymph node and distant metastasis was observed.

Diagnosis: Histopathological analysis revealed large atypical epithelial cells in upper ureter mass, based on neuroendocrine morphology. Immunohistochemistry was positive for synaptophysin, CD 56, and cytokeratin. Accordingly, the upper ureter mass was finally diagnosed as LCNEC stage III, pT3 cN0 cM0.

Intervention: Right nephroureterectomy was conducted.

Outcomes: Multiple metastatic lesions were detected in the right adrenal, paracaval, and right pararenal space of the patient in a CT scan 3 months post-surgery. The patient chemotherapy and radiation therapy were proceeded for metastatic and recurred mass. But patient died by multiorgan failure

Lessons: In summary, this case study demonstrated that LCNEC can develop even in the upper ureter for the first time, despite the absence of neuroendocrine cells in the normal urothelium. The occurrence of LCNEC in the ureter is still very rare but is possible. Therefore, further studies are needed to establish appropriate treatment strategies.

Abbreviations: CT = computed tomography, EGD = esophagogastroduodenoscopy, LCNEC = large-cell neuroendocrine carcinoma, NE = neuroepithelial, NEC = neuroepithelial carcinoma, PET = positron emitting tomography, SCC = small cell carcinoma, TB = tuberculosis, UVJ = ureterovesical junction.

Keywords: large cell neuroendocrine carcinoma, nephroureterectomy, ureter cancer

1. Introduction

Large cell neuroendocrine carcinoma (LCNEC) is a malignant tumor and is predominantly detected in the lung or gastrointestinal

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Informed written consent was obtained from the patient's son for publication of this case report and accompanying images.

The authors have no conflicts of interest to disclose.

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tract. In addition, primary LCNEC is known to be very rare in the urinary tract. A prior study reported a case of primary LCNEC in the urinary tract occurring mainly in the bladder.^[1] A case highlighting the penetration of LCNEC to the lower ureter has been previously reported.^[2] As it is difficult to detect LCNEC penetrating into the ureter before surgery, histopathological examination should be conducted after surgery. In the absence of published literature, the progress, treatment, prognosis, and risk factors of the disease have yet to be investigated.^[3] Moreover, studies involving LCNEC penetration into the upper ureter have yet to be reported. We present a recent case report from our institution illustrating the unique characteristics of the disease.

1.1. Ethical review

We obtained approval for the research from the Gyeongsang National University Hospital institutional review board.

2. Case report

2.1. Presenting concerns and clinical findings

A 58-year-old Asian female patient was admitted to hospital due to right hydronephrosis and upper ureter mass accidentally detected during her medical examination. In accordance with the

past medical history, she had no hematuria or abdominal pain. She had been treated for pulmonary tuberculosis (TB) at age 12. In addition, she was diagnosed with hypertension 8 years ago and was treated with antihypertensive drugs. She had been hospitalized for rib fracture in the past, but had no history of operative treatment. There were no unusual findings in terms of her family history. She did not drink or smoke. Physical examination showed normal vital signs, without any abdominal or costo-vertebral angle tenderness.

Laboratory findings revealed a slight increase in white blood cells and lactate dehydrogenase up to $10,910/\text{mm}^3$ and 293 U/L as a result of complete blood count and biochemical examination, respectively. Urinalysis indicated both red blood cells and white blood cell count within the normal range. Acid-fast bacilli staining of sputum sample yielded negative results. Urine cytology examination revealed no malignant cells.

The clinical profile of the patient was obtained from the electronic medical records of our institution.

2.2. Timeline

We have described timeline in Figure 1.

2.3. Diagnostic focus and assessment

Chest X-ray revealed calcified nodular lesions in the right upper lung field, suggesting previous traces of pulmonary TB. The computed tomography (CT) scan showed enhancing mass approximately 3.3 cm in size in the right upper ureter, which caused severe hydronephrosis in the right renal pelvis and upper ureter (Fig. 2A and B), without any lymph node enlargement or metastasis to other organs. Moreover, there were no findings of suspected metastasis in the right ureter.

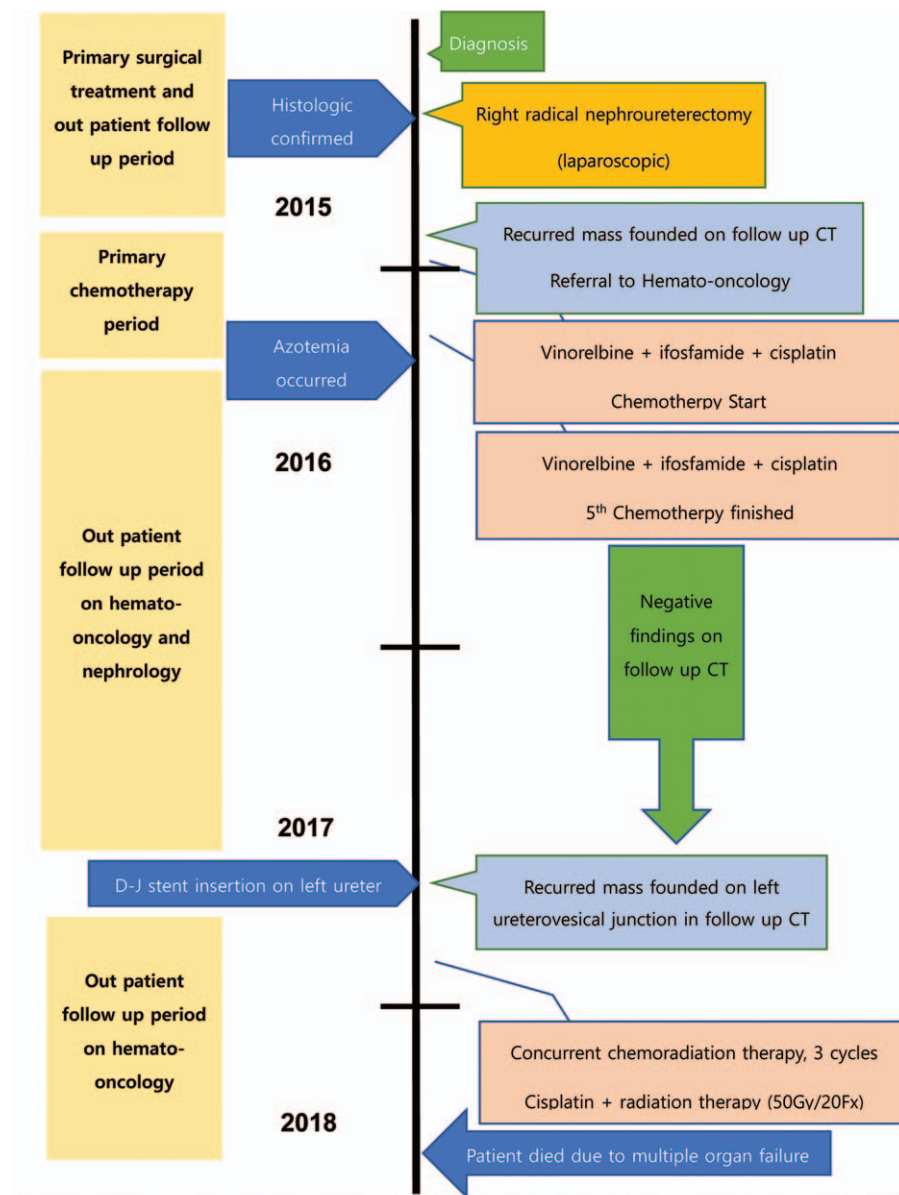


Figure 1. Timeline of patient outcomes.

Cystoscopy results indicated no unusual findings in the bladder. However, a tumor obstructing the entire right upper ureter was found after ureteroscopy.

Pathologic gross findings showed a kidney covered with fatty tissues and approximately 20 cm-long ureter. Specifically, hydronephrosis and tumor were detected in the kidney and the thickened part of the ureter, respectively. This tumor obstructed the ureter lumen. The ureter tumor measured 3.5×4 cm in size. Hematoxylin and eosin staining was also conducted with the excised kidney and the fragment of ureteral tumor. In addition, immunohistochemical staining of p16, p53, vimentin, desmin, cytokeratin, CD38, CD138, CD56, CD99, S-100, HMB45, epithelial membrane antigen, CD3, CD20, synaptophysin, and thyroid transcription factor-1 was carried out.

Microscopic findings showed tumor penetration into the periureteral fat tissue, but not to the renal vein. In addition, we found negative ureteral and circumferential resection margins. Histologically, ureteral tumors showed a diffuse or vaguely nesting growth pattern and focal necrosis. The tumor cells were polygonal and contained a moderate amount of cytoplasm. The nuclei were large and hyperchromatic, and contained small nucleoli (Fig. 3A). In addition, numerous mitotic figures (per more than 20 high-power fields) were found in the tumor.

Immunohistochemistry showed positive results for cytokeratin (Fig. 3B), CD 56 (Fig. 3D), and synaptophysin (Fig. 3E) as well as vimentin (Fig. 3C) suggesting sarcomatous changes. Thyroid transcription factor-1 was expressed in focal areas (Fig. 3F). The patient tested positive for p53, and slightly positive for p16. However the other immunohistochemical staining negative (Table 1). The patient was finally diagnosed with LCNEC.

In the Department of Pathology of our institution, physicians considered the possibility of metastatic LCNEC associated with the gastrointestinal or respiratory tract, and therefore, conducted chest CT, positron emitting tomography (PET), esophagogastroduodenoscopy (EGD), colonoscopy, colposcopy, and punch biopsy, to determine the primary lesion. The chest CT results indicated several small indeterminate nodules in the right upper and middle lobes, and a small calcific granuloma was found in the right upper lobe. By contrast, PET scan revealed no fluorodeoxyglucose uptake in the small nodule of the upper lobe or the right middle lobe of the right lung. Accordingly, the lesion detected by chest CT was considered to be a prior trace of pulmonary TB. EGD findings suggested atrophic gastritis and intestinal meta-

Table 1**Results of immunohistochemical stain.**

P16	Positive, weakly
P53	Positive
Vimentin	Positive
Desmin	Negative
Cytokeratin	Focally positive
CD38	Negative
CD138	Negative
CD56	Positive
CD99	Negative
S-100 protein	Negative
HMB45	Negative
Epithelial membrane antigen	Negative
CD3	Negative
CD20	Negative
Synaptophysin	Positive
Thyroid transcription factor-1	Focally positive

plasia without any suspected lesions. Polyps were found during colonoscopy, and biopsy confirmed intraepithelial neoplasm. Histologically, polyps showed chronic active inflammation following colposcopy and punch biopsy. Therefore, the LCNEC was finally diagnosed as primary LCNEC ureter tumor, stage III (pT3 cN0 cM0).

2.4. Therapeutic focus and assessment

We diagnosed it as a right upper ureter tumor and performed laparoscopic right nephroureterectomy for complete tumor resection.

2.5. Follow-up and outcomes

Multiple metastatic lesions were detected in the right adrenal, paracaval, and right pararenal space during CT scans performed 3 months after surgery. The patient was treated with chemotherapy regimen of vinorelbine (3100 mg), ifosfamide (155 mg), and cisplatin (65 mg) by 5 cycles. The pararenal space metastatic lesion is improved but not to paracaval metastatic lesion and azotemia occurred after chemotherapy. So the patient treated and followed up by nephrologist after that. New metastatic lesion was detected in the right ureterovesical junction (UVJ) after 18

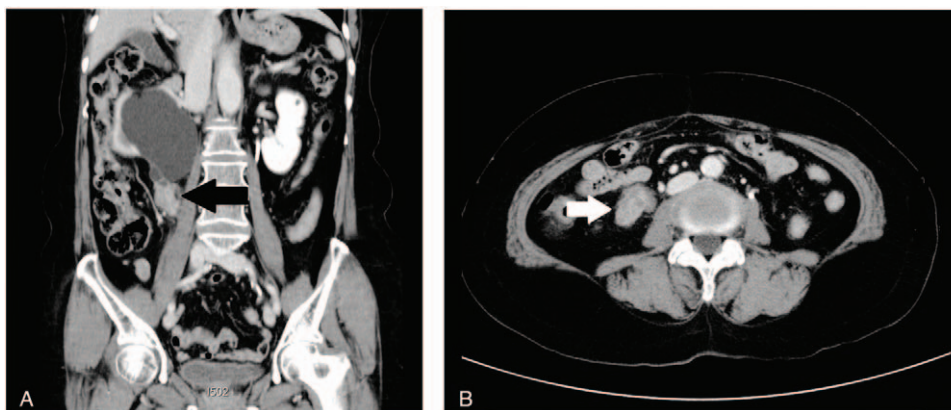


Figure 2. Computed tomographic images of the ureter tumor. (A) Right upper ureteral mass (black arrow) with severe hydronephrosis in coronal section. (B) Right upper ureter enhancing mass (white arrow) in transverse section.

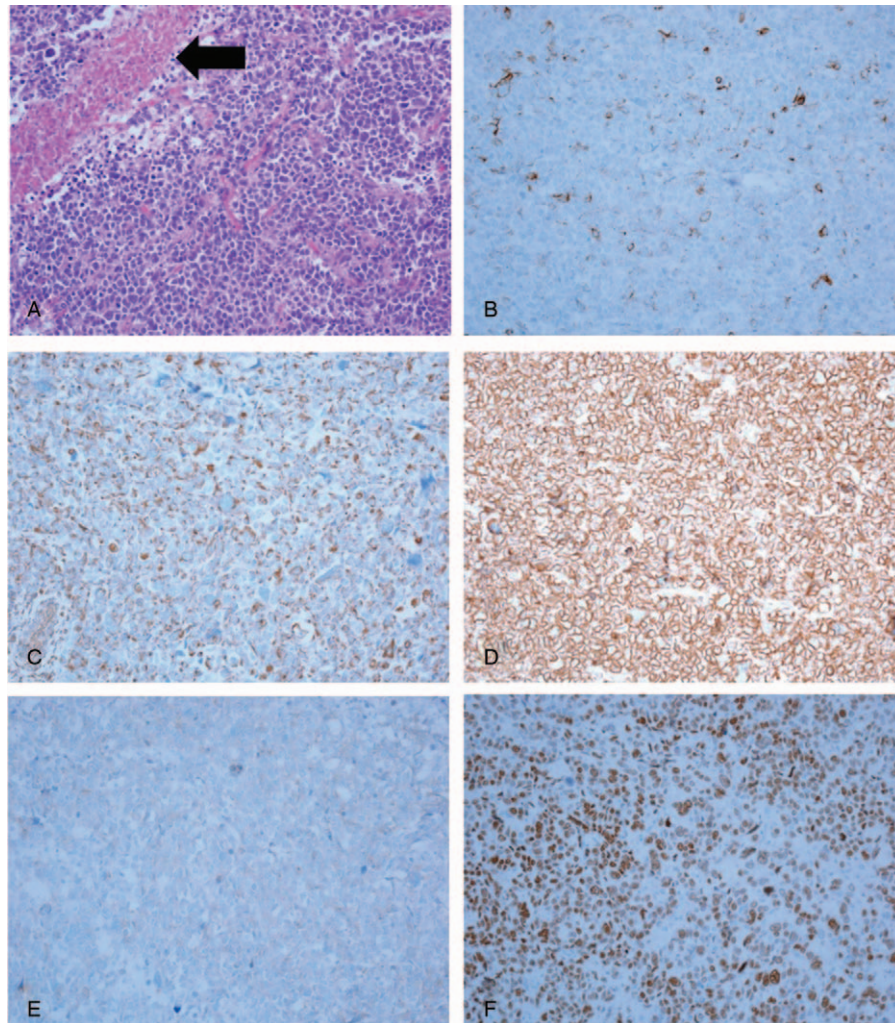


Figure 3. Microscopic findings and immunohistochemical results of large-cell neuroendocrine carcinoma. The tumor shows diffuse or vaguely nesting growth patterns and focal necrosis (arrow). The tumor cells are polygonal and contain moderate amounts of cytoplasm. (A) The nuclei are large and hyperchromatic and show small nucleoli. (B) Scattered cytokeratin-positive cells. (C) The tumor cells are positive for vimentin and (D) CD56 and (E) positive for synaptophysin. (F) TTF-1 is expressed in focal areas.

months. The patient was treated with a chemotherapy regimen of cisplatin (65 mg) and conservative radiation therapy (50Gy/20Fx) on right UVJ mass. But, the patient was showed disease progression and died after 9 months later by multiple organ failure.

3. Discussion

Neuroendocrine tumors originate from neural crest cells and are classified into neural (paraganglioma, neuroblastoma) and epithelial types.^[4] The epithelial type includes well-differentiated neuroepithelial (NE) tumor (carcinoid), well-differentiated NE carcinoma, and poorly-differentiated NE tumor (small cell carcinoma [SCC], LCNEC). They are mainly diagnosed based on histopathology and immunohistochemistry.

Histologically, carcinoid tumors are characterized by polygonal tumor cells, vague cell boundaries, round and regular nuclei, rare mitotic figures, and atypical cells. They test positive for NE markers such as chromogranin A, synaptophysin, and CD56. SCC and LCNEC represent malignant tumors, which are

characterized by increased mitosis, vascular emboli, and tumor necrosis.^[5,6]

However, LCNEC is predominantly located in the gastrointestinal or respiratory tract and is very rarely found in the urinary tract. Furthermore, it has been reported that most LCNECs detected in the urinary tract develop in the bladder and kidney.^[2]

As normal neuroendocrine cells are not found in the urinary tract,^[7] tumor pathogenesis in the ureter is still disputed. Several hypotheses have been proposed to explain the development of ureteral tumors: (1) Development of neuroendocrine metaplasia in the urothelial carcinomatous lesion; (2) malignant transformation of neuroendocrine cells in the urinary tract; (3) malignant changes in neural crest-derived cells locked in the ureter during embryogenesis; and (4) differentiation of stem cells into neuroendocrine lineages.^[7,8] However, these types of tumor are very rare, which explains the challenges involved in proving these hypotheses.

In addition, neuroendocrine carcinomas rarely develop in the ureter. Screening is complicated by the absence of specific symptoms other than ureter obstruction or hematuria.^[9]

Accordingly, these carcinomas are frequently diagnosed at an advanced stage.^[10]

The patient in this case report had no hematuria or abdominal pain and was diagnosed with pT3. Following nephroureterectomy, cisplatin-based chemotherapy was administered to treat tumor recurrence around the relevant sites. However, the survival rate, prognosis, and risk factors after surgery of this rare entity are not well known. Under these conditions, patient management, and prognosis and life expectancy were difficult to calculate.

In summary, this case study demonstrated that LCNEC can develop even in the upper ureter for the first time, despite the absence of neuroendocrine cells in the normal urothelium. The occurrence of LCNEC in the ureter is still very rare but is possible. Therefore, further studies are needed to establish appropriate treatment strategies.

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