

Small Cell Carcinoma of the Ureter with Squamous Cell and Transitional Cell Carcinomatous Components associated with Ureteral Stone

We report a case of primary small cell carcinoma of the ureter with squamous cell and transitional cell carcinomatous components associated with ureteral stone, which is unique in that the patient has remained free of tumor recurrence for 36 months after the surgery without adjuvant chemotherapy or radiotherapy. A 60-yr-old man presented himself with a right flank pain. Computed tomography revealed an ill-defined mass and a stone in the lower one third of the right ureter, and hydronephroureterosis above the stone-impacted site. The patient underwent right nephroureterectomy and stone removal. Upon gross examination, a 3.8 × 1.8 × 1.2 cm white and partly yellow mass was noted in the anterior part of the ureter, resulting in indentation of the ureteral lumen on the posterior side. Light microscopic examination revealed that the mass was mainly composed of small cell carcinoma, and partly squamous cell and transitional cell carcinomatous components. The overlying ureteral mucosa and renal pelvis also contained multifocal dysplastic transitional epithelium and transitional cell carcinoma in situ. There was no vascular invasion, and the surgical margins were free of tumor. The small cell carcinomatous component was positive for chromogranin, neuron specific enolase, synaptophysin, and pancytokeratin but negative for high molecular-weight cytokeratin (K-903) by immunohistochemistry.

Key Words : Carcinoma, Small Cell; Carcinoma, Squamous Cell; Carcinoma, Transitional Cell; Ureteral Calculi

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INTRODUCTION

The occurrence of extrapulmonary small cell carcinoma has been reported in a variety of organs (1). Small cell carcinoma of the genitourinary tract is rarely encountered in the renal parenchyma (2), renal pelvis (3), ureter (4, 5), urinary bladder (6), urethra (7), and prostate (8). Especially, small cell carcinoma of the ureter itself is extremely rare, except for that of the renal pelvis including ureteropelvic junction (9) and only two cases have been reported in the previous literature (4, 5). The histogenesis of this tumor remains uncertain, although several hypotheses have been suggested. Moreover, due to its rarity, the clinical behavior of small cell carcinoma of the ureter has not been well established.

In this paper, we report the clinical characteristics, pathological features, and immunohistochemical results in a case of small cell carcinoma combined with squamous cell and transitional cell carcinomatous components which was associated with ureteral stone.

CASE REPORT

A 60-yr-old man without significant prior medical history presented himself with a 2-weeks history of right flank pain in September 1998. At admission, he complained of urinary frequency, hesitancy, and dysuria. However, he had no history of gross hematuria. After admission, his flank pain partially subsided, but the urinary frequency, hesitancy, dysuria, and sense of residual urine persisted. He had a smoking history of about or less than 0.5 pack per day, and he denied any respiratory symptoms. Physical examination was unremarkable except for a soft, nontender mass palpated in his right upper abdomen. All laboratory investigations, including complete blood cell count, biochemical parameters, and urinalysis, yielded values within normal limits. ^{99m}Tc-labeled dimercaptosuccinic acid scan revealed no uptake in the right kidney. Chest radiography and plain radiography of the kidney, ureter, and urinary bladder (KUB) revealed no remarkable findings except for a radiopaque density in the right pelvic cavity (Fig. 1A). Abdominal computed

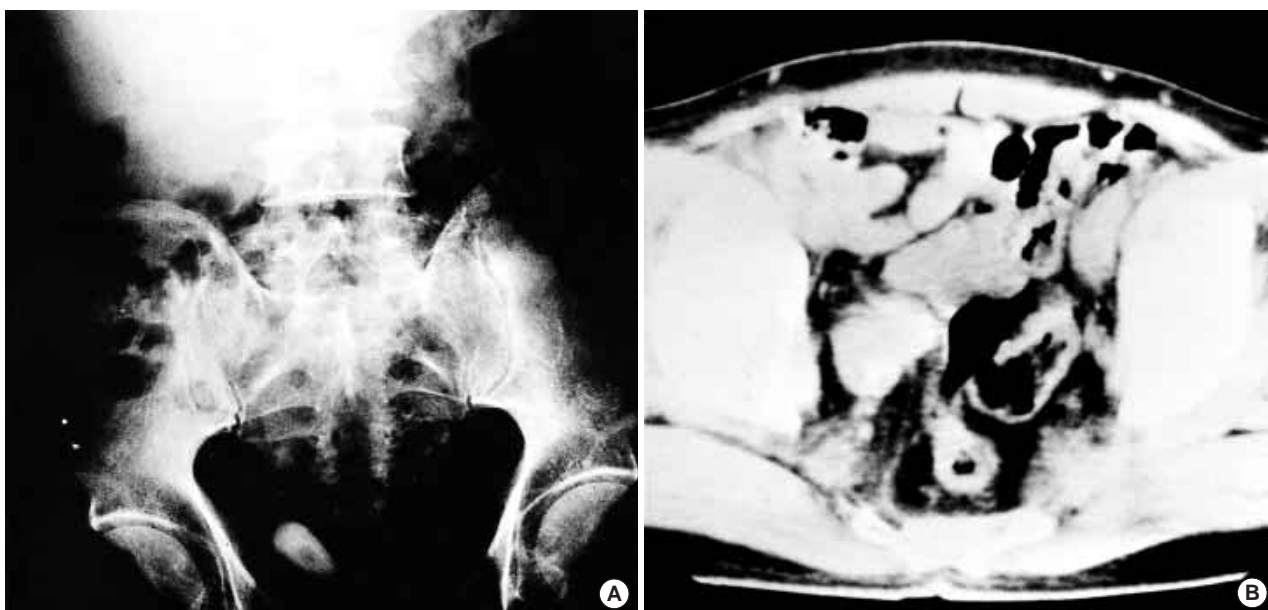


Fig. 1. Simple KUB shows a radiopaque stone in right distal ureter (A). Computed tomographic scan shows an ill-defined, low-density mass in the right distal ureter resulting in irregular thickening of the ureteral wall and obliteration of the ureteral lumen just above the stone-impacted site (B).

tomography (CT) revealed right hydronephroureterosis and a stone in the right distal ureter with an irregularly thickened ureteral wall just above the stone-impacted site (Fig. 1B). However, neither a definite ureteral mass nor enlarged pelvic lymph nodes were identified on CT scans. Based on the imaging findings, right nephroureterectomy with stone removal was performed on the patient. A palpable mass, which was found in the distal anterior ureter just above the stone-impacted site during the operation, was sent for frozen section evaluation. The pathologic findings of frozen and permanent sections are described below. The patient refused either adjuvant chemotherapy or radiotherapy. He has been well without evidence of tumor recurrence or metastasis for 36 months after surgery.

Gross examination of the right nephroureterectomy specimen revealed a hydronephrotic kidney with a dilated renal pelvis and calyces with renal cortical thinning, and ureteral dilation. A segment of the right distal ureter contained an ill-defined, ovoid mass ($3.8 \times 1.8 \times 1.2$ cm) that protruded into the ureteral lumen and caused partial obliteration of the ureter. The cut surface of the mass was grayish-white with patchy yellow areas and small hemorrhagic foci (Fig. 2A). The mass in the anterior side of the ureter indented the ureteral lumen on the posterior side. Upon light microscopic examination of the mass, various malignant epithelial components including small cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma were observed. The ureteral lumen was almost totally occluded by the small cell carcinomatous component, located mainly in the anterior side of the ureter (Fig. 2B). The squamous cell and tran-

sitional cell carcinomatous components were seen especially on the posterior side of the ureter (Fig. 2C, D). Three tumor components were intermingled on the lateral and posterior side of the ureter and a gradual transition of small cell carcinoma to transitional cell and squamous cell carcinoma was noted. The tumor invaded throughout the proper muscle of the ureter, but resection margins were free of tumor. There was no vascular invasion. The overlying ureteral mucosa of the tumor was almost entirely denuded, and several foci of dysplastic transitional epithelium and transitional cell carcinoma in situ were found (Fig. 2E). The renal pelvis also showed focal transitional cell carcinoma in situ. The overlying ureteral lumen of the tumor was focally covered with squamous cell carcinoma but the transition from transitional cell carcinoma in situ was not found due to ureteral mucosal denudation. The renal parenchyma had interstitial inflammation and fibrosis with glomerular sclerosis but no evidence of tumor. Immunohistochemical staining for chromogranin showed strong reactivity in the small cell carcinomatous component (Fig. 2F), but not in the squamous cell and transitional cell carcinomatous components. Immunohistochemical staining for another neuroendocrine markers including neuron specific enolase and synaptophysin was also positive in small cell carcinomatous component. High molecular-weight cytokeratin (K-903) staining revealed strong reactivity in the cytoplasm of the transitional cell carcinomatous component, weak reactivity in the squamous cell carcinomatous component, but no reactivity in the small cell carcinomatous component. Pancytokeratin was present in all three tumorous components.

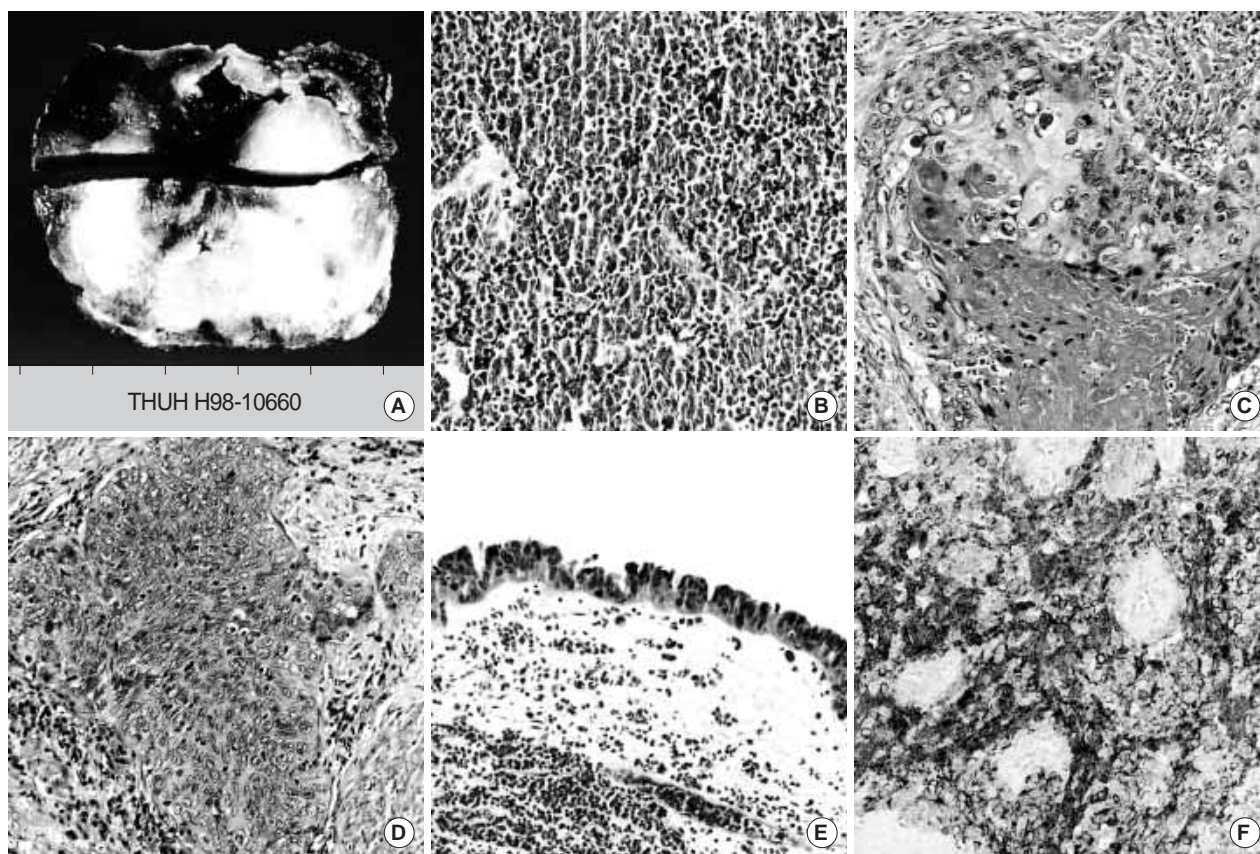


Fig. 2. On gross examination, cut surface of the right ureter shows the luminal narrowing caused by intramural infiltrative mass, which mainly involved the anterior half (A). On light microscopic examination, the tumor is mainly composed of small cell carcinomatous component, which shows densely packed small round tumor cells with hyperchromatic nuclei, scanty cytoplasm with delicate stroma (B). The squamous cell (C) and transitional cell (D) carcinomatous components are intermingled. The overlying ureteral mucosa of the tumor shows multifocal dysplastic transitional epithelium and transitional carcinoma in situ (E) with almost entire denudation. Immunohistochemical staining for chromogranin shows positive reactivity only in the small cell carcinomatous component (F) (B-F, $\times 200$).

DISCUSSION

The majority of small cell carcinomas of the genitourinary tract occur in combination with other tumorous components, such as transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma. Its variable histologic feature supports the notion that small cell carcinoma in any sites of the urinary tract, including renal pelvis (3), urinary bladder (6), and ureter (4, 5), originates from multipotential stem cells. Also in this case, small cell carcinoma appeared with squamous cell and transitional cell carcinomatous components, which is in agreement with the hypothesis that this tumor probably originates from multipotential stem cells of the ureter. Two previously reported cases of small cell carcinoma of the ureter also had other tumorous components; one had transitional cell carcinoma (4), and the other leiomyosarcomatous and chondrosarcomatous elements, in addition to transitional cell and squamous cell carcinomatous, and adenocarcinomatous components (5) (Table 1). The other hypothesis is that small cell carcinoma originates from intrinsic neuro-

endocrine cells within the normal genitourinary tract, derived from the neural crest during the embryogenesis. It was reported that a few number of neuroendocrine cells have been noted in the normal urinary tract including the renal pelvis (11), ureter (11), urinary bladder (12), urethra (13), and prostate (14), which are derived from mesonephros. However, this theory does not support two previously reported cases, which showed combined histologic features of other carcinomatous components without exception (4, 5). It has also been reported that no neuroendocrine cells were noted in the normal renal parenchyma (15), which is derived from metanephros.

The most common symptom of small cell carcinoma of the ureter is gross hematuria, which is also seen in small cell carcinomas at other sites of the urinary tract (6). In the previous report (4, 5), asymptomatic gross hematuria was the initial symptom of small cell carcinoma of the ureter without exception. Our patient presented with flank pain without gross hematuria. An ill-defined ureteral mass seen on radiological findings was initially interpreted as a periureter-

Table 1. The characteristics of reported cases of small cell carcinoma of the ureter

Characteristic	Sakai <i>et al.</i>	Tsutsumi <i>et al.</i>	Present Case
Age (yr)	62	60	60
Sex	M	M	M
Initial symptom	Gross hematuria	Gross hematuria	Right flank pain
Site in ureter	Left upper 1/3	Right lower 1/3	Right lower 1/3
Size	1.8 × 1.8 × 5.0 cm	≤ 8 cm	1.2 × 1.8 × 3.8 cm
Main component	SCC	SCC	SCC
Neuroendocrine marker	NSE (+)	NSE (+) Chromogranin (-)	NSE (+) Chromogranin (+) Synaptophysin (+)
Combined components	TCC	TCC+SqCC+AC+CS+LS	TCC+SqCC
Treatment	Surgery	Surgery+Radiation	Surgery
Adjuvant therapy	Chemotherapy	Chemotherapy	None
Follow-up duration	12 months	24 months	36 months
Follow-up result	NED	DOD	NED

SCC, small cell carcinoma; NSE, neuron specific enolase; TCC, transitional cell carcinoma; SqCC, squamous cell carcinoma; AC, adenocarcinoma; CS, chondrosarcoma; LS, leiomyosarcoma; NED, no evidence of disease; DOD, dead of disease (bone and liver metastasis).

al inflammatory lesion, because the ureteral stone impacted upon the ureteral lumen. It is of note that our patient sought treatment earlier due to the presence of an ureteral stone than the patients in previously reported cases, which may explain why the outcome for this patient was favorable. There have been few reports that carcinomas of the urinary tract at the stone-impacted sites during long-term follow-up (16). It has been also proposed that chronic mechanical irritation by stone may induce morphological changes of the transitional epithelium including dysplastic changes might lead to carcinoma of the urinary tract (17). Primary squamous cell carcinoma of the ureter associated with ureteral stone has been already reported (18).

It has also been suggested that smoking is related to the carcinogenesis of small cell carcinoma in extrapulmonary areas, especially the genitourinary tract (19, 20). It has been reported that small cell carcinomas of the urinary tract including kidney (21), renal pelvis (3), urinary bladder (22), and prostate (21) have developed in heavy smokers. Our patient had a smoking history of less than 0.5 pack per day for 30 yr and it has also been reported that cases of small cell carcinoma occurs in any site of the genitourinary tract in non-smokers (8, 21, 22). Therefore, the role of cigarette smoking in the development of small cell carcinoma of the ureter and other extrapulmonary sites remains undetermined. In this case, the patient had neither respiratory symptoms nor remarkable findings by chest radiography. In addition, only one case of metastatic small cell carcinoma of the lung to the ureter has been reported (23). Therefore, the possibility of metastatic small cell carcinoma of the lung to the ureter was not taken into consideration in our case.

The treatment and prognosis of small cell carcinoma of the ureter are not well established (9) because of its rarity (4, 5). Many clinicians have proposed that multimodality therapy which includes surgery, radiation, and chemotherapy is essential for patients with small cell carcinoma of the

urinary tract (3, 6, 9). It has been reported that combined chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) is effective against small cell carcinomas of the genitourinary tract (24). However, it is difficult to determine the most effective therapeutic modality for small cell carcinoma in the ureter because of the small number of reported cases (9).

The majority of small cell carcinomas of the genitourinary tract progress rapidly to the regional lymph nodes, liver, and other organs (21). So the majority of patients with small cell carcinoma die of the disease within a year (7). However, some cases of small cell carcinomas in the renal pelvis and urinary bladder showed relatively slow growth in the primary sites (10).

In summary, we report upon a unique case of small cell carcinoma of the ureter combined with squamous cell and transitional cell carcinomatous components, associated with ureteral stone. The patient is getting well 36 months after the surgery without any adjuvant therapy.

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