A Retrospective Immunohistochemical and Clinicopathological Study of Small Cell Carcinomas of the Urinary Tract

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Background: To investigate the immunohistochemical and clinicopathological behaviors of primary urinary tract small cell carcinomas (SCCs).

Methods: A retrospective study of 10 cases of urinary tract SCC (7 men and 3 women, average age, 54; range, 35-78 years) at Chang Gung Memorial Hospital is reported. Among these cases, 3 tumors arose from the kidney, 2 from the renal pelvis, 2 from the ureter, and 3 from the bladder. Clinical and follow-up data were obtained. Histological and immunohistochemical studies with antibodies to neuroendocrine (NE) markers were conducted.

Results: The most prominent common feature of the 10 SCCs was their cell histopathology: small to medium-sized round to spindle-shaped cells with scanty cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli. Immunostaining revealed positive neuron-specific enolase (NSE) reactivity in 10 of 10 tumors, but there was focal and weak staining for chromogranin-A (CgA) in 4 of 10 tumors. The 7 patients with vimentin-positive SCCs all developed metastatic lesions, and 5 of them expired within 1 year.

Conclusions: SCCs of the urinary tract system share similar histopathological features and NE markers with their pulmonary counterpart. NSE was expressed more consistently than CgA in these tumors. However, the preferential expression of NSE and intensity of immunostaining of these 2 NE markers did not predict the clinical outcome of these patients. The presence of both SCC and transitional cell carcinoma or SCC alone did not foretell the clinical outcome either. Patients with the presence of vimentin in the tumor tissues appeared to have poorer prognoses with early metastasis and mortality.

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Key words: small cell carcinoma, kidney, urinary bladder, transitional cell carcinoma, neuroendocrine markers.

Extrapulmonary small cell carcinomas (SCCs) are generally malignant, and occur rarely with a reported incidence of 0.1% to 0.4%. There have been about 180 cases of genitourinary SCCs reported in the literature, most of which occurred at sites in the bladder, prostate, kidney, and ureter. The overall median survival was 10.5 months. In the genitourinary tract, SCCs of the prostate have a poor prognosis, while SCCs of the urinary bladder seem to have a better prognosis if diagnoses are made at an early stage. Small cell renal carcinomas are more malignant and fatal compared to non-SCCs of

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the kidney.(4) Extrapulmonary SCCs are very similar to small cell lung cancers with respect to histopathology and the expression of neuroendocrine (NE) markers. In this report, we investigated the immunohistochemical features and reviewed the clinicopathological behaviors of 10 cases of urinary tract primary SCC seen at Chang Gung Memorial Hospital.

METHODS

Ten cases of primary SCC of the urinary system were collected from the tumor registry at Chang Gung Memorial Hospital between 1988 and 1999. The medical records were reviewed, and clinical and follow-up data were obtained. The pathological diagnosis for SCC fulfilled the criteria set forth by the World Health Organization in all cases. The renal tumors were staged based on Robson's criteria; renal pelvis, ureter, and bladder tumors were staged based on the Jewett-Marshall scheme. Immunohistochemical staining was performed on sections of 10 formalin-fixed, paraffin-embedded tissues using the avidin-biotin peroxidase complex (ABC) method. The Vectastain ABC kit was provided by Vector Laboratories (Burlingame, CA). Tissue sections were stained with a panel of monoclonal and polyclonal antibodies. The sources of these antibodies and the designations of hybridoma clones from which monoclonal antibodies (MAbs) were generated are listed in Table 1. The stainability of these antibodies is known not to be affected by either formalin fixation or paraffin embedding.

Table 1. Monoclonal Antibodies Used in Immunostaining

<table>
<thead>
<tr>
<th>Monoclonal antibody to</th>
<th>Clone</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE</td>
<td>BBS/NC VI H14</td>
<td>Signet</td>
</tr>
<tr>
<td>Chromogranin-A</td>
<td>LK2 H10</td>
<td>Signet</td>
</tr>
<tr>
<td>EMA</td>
<td>E29</td>
<td>DAKO</td>
</tr>
<tr>
<td>AE1/AE3</td>
<td>AE1/AE3</td>
<td>Signet</td>
</tr>
<tr>
<td>Vimentin</td>
<td>V9</td>
<td>DAKO</td>
</tr>
<tr>
<td>S100 α</td>
<td>SH-A1</td>
<td>Sigma</td>
</tr>
<tr>
<td>S100 β</td>
<td>SH-B1</td>
<td>Sigma</td>
</tr>
<tr>
<td>LCA</td>
<td>T29/33</td>
<td>DAKO</td>
</tr>
</tbody>
</table>

NSE: neuron-specific enolase; EMA: epithelial membrane antigen; AE1/AE3: AE1 reactive with primary low and intermediate type I acidic keratins (40, 48, 50, and 56.5 kD), AE3 reactive with primary high-molecular-weight keratins (52, 54, 56, 58, 59, 64, and 65-67 kD) of the type II basic subfamily; LCA, leukocyte common antigen.

RESULTS

Clinicopathological characteristics. The clinical data on patients are summarized in Table 2. Patient age at presentation, gender, location and stage of the disease, clinical symptoms, type of management, site of metastasis, follow-up duration, and cause of death were noted.

There were 7 male and 3 female patients; the average age of all patients at presentation was 54 (range, 35-78) years. Of the 10 patients, 3 had tumors arising from the kidney, 2 from the renal pelvis, 2 from the ureter, and 3 from the urinary bladder. There was no prostatic SCC in this report. The chief complaint of those patients with renal pelvis, ureter, or bladder tumors was gross hematuria. Patients with renal tumors presented with flank pain, body weight loss, and palpable abdominal masses.

Of the renal tumors in 3 patients, 2 were stage III, and the other patient had tumor invasion of the abdominal wall (stage IV) (Fig. 1). A radical nephrectomy was performed in these patients, followed by adjuvant chemotherapy with cyclophosphamide, epidoxorubicin, and vincristin. Unfortunately, these patients developed early metastases, and 2 expired within 9 months. Of the 3 patients with renal pelvis tumors, 2 whose tumors were at stage D expired 6 months after the operation; the other patient with a stage B tumor (case 5) developed multiple metastases (lung, bone, and lymphoma).
nodes) and survived for 31 months after a nephroureterectomy. In the 2 patients with ureter tumors, 1 had a ureteral stone, and a superficial tumor was found simultaneously. He received a nephroureterectomy but developed neck lymph node metastasis and expired 17 months later. Another patient, who had previously received segmental resection of his ureter due to in situ carcinoma, had a recurrent ureteral tumor (stage C), and was disease-free for 55 months after a nephroureterectomy. The 3 patients in the bladder tumor group had an average age of 74 (range, 69-78) years, which was much older than the other groups. One patient was diagnosed with a stage D1 tumor, and received palliative transurethral resection of the bladder tumor due to hematuria. He passed away 3 months later. A partial cystectomy was performed on the patient with a stage C tumor, and this patient expired 7 months after the operation because of respiratory failure. The third patient with a stage B tumor is still being followed-up after a radical cystectomy.

Most of the patients developed early metastases (Table 2). The preferential sites for metastasis were the lungs and lymph nodes, and occurred in 5 patients. Other frequent metastatic sites were bone and liver.

**Histological characteristics.** The renal tumors were mostly large in size, measuring up to $20 \times 10 \times 8 \text{ cm}$ with central necrosis (Fig. 1), and the renal pelvis tumors, also appearing as large tumor masses, were often found to have invaded the renal parenchyma.

### Table 2. Clinicopathological Summary

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Primary site</th>
<th>Pathological stage/grade</th>
<th>Presenting symptoms</th>
<th>Management</th>
<th>Metastatic sites</th>
<th>Follow-up (mo)</th>
<th>Outcome of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5M</td>
<td>45</td>
<td>Kidney</td>
<td>III</td>
<td>Mass/pain</td>
<td>Nephrectomy</td>
<td>Liver/LN</td>
<td>8</td>
<td>Suicide</td>
</tr>
<tr>
<td>2</td>
<td>2M</td>
<td>42</td>
<td>Kidney</td>
<td>III</td>
<td>Mass/wt loss</td>
<td>Nephrectomy</td>
<td>Lung/LN</td>
<td>12</td>
<td>LFU</td>
</tr>
<tr>
<td>3</td>
<td>4F</td>
<td>35</td>
<td>Kidney</td>
<td>IV</td>
<td>Mass/pain</td>
<td>Nephrectomy</td>
<td>Lung</td>
<td>9</td>
<td>DOD</td>
</tr>
<tr>
<td>4</td>
<td>5M</td>
<td>42</td>
<td>Renal pelvis</td>
<td>D/3</td>
<td>Hematuria</td>
<td>Neph-ure.</td>
<td>Lung</td>
<td>6</td>
<td>DOD</td>
</tr>
<tr>
<td>5</td>
<td>4F</td>
<td>44</td>
<td>Renal pelvis</td>
<td>B/3</td>
<td>Hematuria/pain</td>
<td>Neph-uret.</td>
<td>Lung/bone/LN</td>
<td>31</td>
<td>DOD</td>
</tr>
<tr>
<td>6</td>
<td>7M</td>
<td>57</td>
<td>Ureter</td>
<td>A/2</td>
<td>Hematuria/pain</td>
<td>Neph-uret.</td>
<td>LN</td>
<td>17</td>
<td>DOD</td>
</tr>
<tr>
<td>7</td>
<td>0M</td>
<td>50</td>
<td>Ureter</td>
<td>C/3</td>
<td>Hematuria</td>
<td>Neph-uret.</td>
<td>&gt; 55</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>7M</td>
<td>75</td>
<td>Bladder</td>
<td>D1/3</td>
<td>Hematuria</td>
<td>TURBT⁹</td>
<td>LN</td>
<td>3</td>
<td>DOD</td>
</tr>
<tr>
<td>9</td>
<td>4F</td>
<td>69</td>
<td>Bladder</td>
<td>B/3</td>
<td>Hematuria</td>
<td>Cystectomy</td>
<td>NED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3F</td>
<td>78</td>
<td>Bladder</td>
<td>C/3</td>
<td>Hematuria</td>
<td>P. cystect</td>
<td>Lung/bone</td>
<td>7</td>
<td>DOD</td>
</tr>
</tbody>
</table>

**Abbreviations:** a: lymph node; b: body weight loss; c: alive with disease; d: lost to follow-up; e: died of disease; f: nephroureterectomy; g: no evidence of disease; h: transurethral resection of a bladder tumor; i: partial cystectomy.

### Table 3. Summary of Immunostaining Results on Tumor Areas

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Histologic features</th>
<th>NSE</th>
<th>CgA</th>
<th>S100α</th>
<th>S100β</th>
<th>AE1/AE3</th>
<th>Vimentin</th>
<th>EMA</th>
<th>LCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SCC</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>SCC</td>
<td>++</td>
<td>+/− focal</td>
<td>NT</td>
<td>NT</td>
<td>+ scattered</td>
<td>+ scattered</td>
<td>+/− focal</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>SCC</td>
<td>++</td>
<td>++</td>
<td>−</td>
<td>+/−</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SCC/TCC</td>
<td>++</td>
<td>+</td>
<td>−</td>
<td>+ scattered</td>
<td>+</td>
<td>−</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>SCC/TCC</td>
<td>++</td>
<td>+/− focal</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>+ focal</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>SCC/TCC</td>
<td>+</td>
<td>+/− focal</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>+ focal</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SCC/TCC</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>SCC</td>
<td>++</td>
<td>−</td>
<td>−</td>
<td>+ scattered</td>
<td>+/− focal</td>
<td>−</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>SCC/TCC</td>
<td>++</td>
<td>−</td>
<td>NT</td>
<td>+</td>
<td>NT</td>
<td>+</td>
<td>−</td>
<td>+/− focal</td>
</tr>
<tr>
<td>10</td>
<td>SCC/TCC</td>
<td>+</td>
<td>−</td>
<td>NT</td>
<td>NT</td>
<td>+ scattered</td>
<td>+/++</td>
<td>−</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** NSE: neuron-specific enolase; CgA: chromogranin-A; EMA: epithelial membrane antigen; LCA: leukocyte common antigen; SCC: small cell carcinoma; TCC: transitional cell carcinoma; NT: not tested.

Results are expressed by: −: negative; +/−: weakly positive; +: moderately positive; ++: strongly positive.
Most of the tumors in the urinary bladder were flat, infiltrating, and necrotic in appearance. The light-microscopic features of the small cell carcinomatous component were similar in all tumors. Most of the tumor cells were small, ovoid to spindle-shaped with hyperchromatic nuclei and scanty cytoplasm (Fig. 2A). In the 6 tumors with a histology of mixed transitional cell carcinoma (TCC) and SCC, tumor nests of the 2 components were found to exist separately in the same tissue. The histology of 1 such tumor (case 9) is depicted in Fig. 2B.

Immunohistochemical features. Immunostaining was performed in the 10 cases for the expression of

![Fig. 2](image1)

**Fig. 2** Small cell carcinoma tumor cells appearing small and ovoid to spindle-shaped with hyperchromatic nuclei and scanty cytoplasm (A) (H & E, ×200). Bladder tumor from case 9 showing both transitional cell carcinoma (left side) and small cell carcinoma (right side) components (B) (H & E, ×400). Note that the 2 cell components exist separately with connective tissue between them.

![Fig. 3](image2)

**Fig. 3** Immunostaining of a small cell carcinoma showing strong, positive NSE reactivity (A), and weak to moderate chromogranin-A reactivity (B). There was stronger positive AE1/AE3 staining in the transitional cell component (2 tumor nests on the left side) as compared with that in the small cell component (right side) (C). Note the nonreactive connective tissue between the tumors (A, B, and C, ×200).
neuron-specific enolase (NSE), chromogranin-A (CgA), cytokeratin AE1/AE3, vimentin, epithelial membrane antigen (EMA), and leukocyte common antigen (LCA), and in 7 cases for S100α and S100β. The results are summarized in Table 3.

Of the 10 SCCs examined, 6 stained strongly (++) , 3 moderately (+), and 1 weakly (+/-) for NSE. As for CgA, 1 stained intensively, 1 moderately, 2 weakly and focally, and the remaining 6 gave negative results. Eight stained moderately, 1 weakly, and 1 negatively for AE1/AE3 (Fig. 3). One tumor intensively stained, 5 moderately stained, 1 weakly stained, and 3 negatively stained for vimentin. Two tumors stained moderately, 3 weakly and focally, and the remaining 5 negatively for EMA. None of the 10 tumor specimens tested gave positive staining results for LCA in tumor areas, signifying that the tumor cells studied were not of a lymphoid nature.

**DISCUSSION**

Extrapulmonary SCCs are rare and rather malignant. Since the first report of such a carcinoma of the mediastinal gland by Duguid in 1930, cases of extrapulmonary SCCs of various organs have been sporadically reported from organs such as the cervix, esophagus, endometrium, skin, prostate, urinary bladder, and kidney as well as other unusual sites. In general, these tumors respond poorly to treatment with chemotherapeutic agents, and the prognosis with these tumors is poor and varies considerably from case to case. For instance, in the genitourinary tract most of the reported SCCs are mainly of the prostate and urinary bladder. SCC of the kidney is more malignant and rapidly fatal as compared with non-SCCs in spite of adjuvant chemotherapy.

We encountered no prostate SCC in our 3 affiliated hospitals during the period from 1988 and 1999. This is not too surprising in view of the fact that there was a low incidence of prostate cancer in Taiwan, with a rate of 14.25/100,000.

Clinically, all patients presented with symptoms of involvement of a specific organ or a few organs. There were no specific clinical indicators that would have directed the attention of clinicians to SCC. SCC is generally diagnosed by its histologic characteristics, which are not dissimilar from those of its pulmonary counterpart. Histologically, tumor cells are small, ovoid to spindle-shaped with hyperchromatic nuclei and scanty cytoplasm. Negative LCA reactivity excludes the possibility of lymphoid cells. Ultrastructurally, SCC cells have been described as having oval, moderately irregular nuclei with dense chromatin peripherally.

The histogenesis of SCC has been controversial. Pearse demonstrated the ability of small cells to synthesize and store amines and to decarboxylate certain amino acids to form amines, and termed these cells APUD (amine precursor uptake and decarboxylation) cells. In urothelial cancers, the presence of both small cell and transitional cell components may imply the multipotential origin of this tumor. It has been proposed that renal SCCs originate from metanephrogenic blastemas or the renal pelvis epithelium. Some investigators believe that these tumors are of multipotential origin, or from "basal" cells with pluripotentialities. In this report, most of the tumors of the urinary bladder, ureter, and renal pelvis (6/10) were of mixed components of high-grade TCC and SCC. The coexistence of these 2 different cell types in the urothelium and the expression of NSE markers in the transitional cell component may indicate that SCC is the most malignant variant of epithelial neoplasms, or that it is likely to have originated from multipotential epithelium with divergent differentiation. In primary renal small cell tumors, the renal parenchyma tissue is often found to be replaced by small, round neuroendocrine tumor cells in varying degrees. This may imply the possibility of the dedifferentiation of renal tubule cells in primary renal SCC. While the presence of a mixed tumor histotype or of SCC alone failed to reveal any prognostic significance, the number of cases in our series is too small to draw a definitive conclusion in this regard.

As found in the pulmonary counterpart, SCCs of the urinary system in our series mostly expressed NSE and less frequently CgA. SCC cells are known to express some NE markers, such as NSE, CgA, bombesin, synaptophysin, and calcitonin. NSE is found in extracts of brain tissue and in APUD cells of the neuroendocrine system and their tumors. NSE, however, has also been identified in some non-neuroendocrine tumors, such as carcinomas, fibroadenomas, and lymphomas. CgA is a constituent of the secretory granules of most peptide-producing endocrine cells, and its presence is usually associated with a number of cytoplasmic-dense core
However, secretory granules in SCC cells seen by electron microscopy do not always accompany the detection of CgA. Negative to focally weak expression of CgA in SCCs (cases 5, 6, and 7) seemed to indicate a better prognosis. The preferential expression of NSE and staining intensity of either of the 2 NE markers by tumor cells did not correlate with the disease status or prognosis of urinary SCCs. However, the number of cases is too small in our series to draw any definitive conclusions. NSE could only be used for the identification of the neuroendocrine component of this tumor.

Seven of the 10 SCC tumors in this study stained positively for vimentin. The 7 patients with vimentin-positive SCCs all developed metastatic lesions, and 5 of them expired within 1 year. Two patients (cases 5 and 7) without vimentin expression in their tumor tissues survived for much longer periods of 31 and over 55 months, respectively. The scattered or focal expression of vimentin in most of our cases (7/10) of urinary SCC is intriguing. While the biologic role of vimentin in SCCs of the urinary tract remains unclear, indirect evidence from clinical observations indicates that neoeexpression of this intermediate microfilament in primary breast carcinomas is associated with an increased rate of metastatic potential. The presence of vimentin may therefore predict a more-aggressive SCC and a graver outcome.

Clinically, SCC progressed rapidly in our patients; 5 patients developed lung metastases, 5 lymph node metastases, 2 bone metastases, and 1 liver metastasis. Three of the 5 patients had lymph node metastases at presentation; 1 developed lung metastasis 6 months after surgery (case 3). Of the 5 patients with lung metastases, 1 developed both bone and lymph node metastases, and 1 developed bone metastasis. Most of the patients died within 1 year after metastasis was detected, despite aggressive adjuvant chemotherapy. Thus, multimodality therapies should be considered, including radical resection followed by early irradiation and chemotherapy. Systemic combination chemotherapy is highly recommended. Ideally, chemosensitivity and extreme drug resistance assays should be performed to select more-effective drugs and at the same time avoid the toxicity of potentially ineffective drugs, respectively. This approach to cancer patient management has gained much attention in recent years.

In conclusion, SCC of the urinary tract is generally rare, but is a highly malignant disease. It has a similar histology to that of its pulmonary counterpart, and possesses NE cell markers such as expression of NSE and/or CgA. The presence of vimentin in urinary small cell tumor tissues appears to indicate a poorer prognosis, and early metastasis tended to develop. The origin of SCC of the urinary tract still remains inconclusive. The presence of both high-grade TCC and SCC components in a tumor tissue may indicate the pleuripotentiality of this tumor or dedifferentiation of the malignant urothelium. However, the prognostic significance is yet to be determined. Diagnosis of SCC depends largely on its histopathologic characteristics and NE markers. Early diagnosis and radical surgery followed by early adjuvant chemotherapy and radiotherapy are still the golden rule for the management of urinary SCCs. Unlike pulmonary SCCs, cultures of small cell carcinomas of the urinary tract are rarely available; thus the establishment of a cell line would be useful for further studies aimed at uncovering the biology of this rare cancer and at elucidating the role of vimentin expression in the aggressiveness and progression of SCCs.

**Acknowledgements**

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**REFERENCES**

泌尿道小細胞癌的回溯性免疫組織化學特性和臨床病理分析

莊正銘 廖順奎

背 景：本研究之目標，在於分析原發性泌尿道小細胞癌的免疫組織化學特性和臨床致病徑之可能關係的回溯性研究。

方 法：我們針對10位長庚紀念醫院原發性泌尿道小細胞癌病人(男性7人，女性3人，年齡從35至78歲，平均54歲)及症狀來源以及追蹤結果做一回溯性研究；其中3例腎癌、2例腎盂、2例輸尿管以及5例均為膀胱。這些腫瘤組織並非做神經外分泌標的之免疫組織化學染色。

結 果：腫瘤最常見的顯著特徵是在細胞組織病理學上，細胞變小至中等大小、少數細胞質的圓形或橢圓形細胞、核染色體多以及核變得不明顯。全部10個腫瘤以免疫染色法均呈現出NSE (neuron-specific enolase)免疫反應，但是CgA (chromogranin-A)染色則是局部性及弱反應的。十個腫瘤組織中性五個出現vimentin，其中有五個病人在診斷一年內即已過逝。

結 論：泌尿道小細胞癌的組織病理學特性和神經內分泌標記與小細胞肺癌有相似之處，在這些腫瘤中，NSE的表現比CgA更具有致性。然而，NSE表現的強度，以及這兩種神經內分泌標記的免疫染色強度，並不能用來預測臨床結果。在腫瘤組織內同時出現小細胞癌/移形細胞癌兩者或單獨的小細胞癌病灶與預後結果無關。有趣的是，腫瘤vimentin呈陽性的病人，其預後較差，並且會有癌細胞早期轉移和病人早死的現象。

(長庚醫誌 2003;26:26-33)

關鍵字：小細胞癌，腎癌，膀胱，移形細胞癌，神經內分泌標記。