CAS CLINIQUE/ CASE REPORT

SMALL CELL NEUROENDOCRINE CARCINOMA OF THE URINARY BLADDER
Report on Two Cases and Review of the Literature

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INTRODUCTION

Small cell carcinoma of the urinary bladder is a rare but highly aggressive malignancy. It was first reported in 1981 and accounts for 0.5% to 1% of malignant bladder tumors [1-4]. The overall median survival is four months for patients who do not receive chemotherapy, regardless of the stage and 15 months for those receiving chemotherapy [5]. The diagnosis has important implications in terms of prognosis, survival and therapeutic approach.

Differential diagnosis includes mainly poorly differentiated urothelial carcinoma and lymphoma, both of which have relatively better prognosis and different therapeutic approach.

CASE REPORTS

Case 1

A 68-year-old gentleman presented for painless gross hematuria. Kidneys and bladder ultrasound showed a 3 x 2 cm sessile polypoid mass in the right postero-lateral bladder wall. Computed tomography scan (CT scan) of the abdomen and pelvis confirmed the presence of the mass, which appeared to invade the whole thickness of the bladder wall. Cystoscopy revealed a large sessile and necrotic tumor. Transurethral resection (TUR) was performed. A diagnosis of pure small cell (Neuroendocrine) carcinoma invading the mucosa and Muscularis propria (pT2) [6] was made.

He was a poor candidate for radical cystectomy due to his cardiovascular condition. Follow-up cystoscopy was performed at 3 months and 6 months post TUR and failed to show any recurrence. One year after the transurethral resection, the painless gross hematuria reappeared. Abdomino-pelvic CT scan showed infiltrative bladder tumor in the right postero-lateral wall with extension to the right seminal vesicle (Clinical T4a) [6]. Transurethral resection was performed and the pathology was similar to that of the tumor resected one year earlier. Metastatic workup showed lung metastases (Clinical Stage IV). He died one month later of massive transmural myocardial infarction.

Case 2

An 83-year-old gentleman, known to have advanced stage prostatic acinar adenocarcinoma, Gleason score 9,
presented for painless gross hematuria. PSA level was 393 ng/dl. Cystoscopy showed a 3 x 4 cm lobulated exophytic polypoid tumor in the left postero-lateral wall of the bladder. Transurethral resection and bilateral orchiectomy were performed. A diagnosis of pure small cell (neuroendocrine) carcinoma invading the mucosa and Muscularis propria (pT2) was made. Re-review of the prostatic biopsies confirmed the diagnosis of high grade prostatic acinar adenocarcinoma. There were no features of neuroendocrine small cell carcinoma in the prostate biopsies.

Chemotherapy and radical cystectomy were not considered as therapeutic options given his age and medical condition. Follow-up cystoscopy 6 months later showed absence of tumor. One year after transurethral resection, gross hematuria reappeared. CT scan of the abdomen and pelvis showed a large sessile polypoid exophytic mass arising from the left postero-lateral bladder wall with circumferential thickening. A large lymph node in the right internal iliac chain measuring 6 x 5 x 5 cm with features of necrosis was also noticed (Clinical Stage IV). Liver appeared normal. Cystoscopy revealed a large polypoid mass arising from the left postero-lateral wall. A second transurethral resection was performed. Pathology was identical to the previous one obtained one year ago. He died three months later.

Pathology findings
All four specimens showed similar microscopic findings: Solid sheet like and nodular neoplastic proliferation of cells with high nucleo-cyttoplasmic ratio and inconspicuous cytoplasm, imparting a “small round blue cell appearance” on low power (Fig. 1 & 2). The neoplasm occupied and infiltrated the Lamina propria (Fig. 1) and the thick smooth muscle bundles of the Muscularis propria (Fig. 2). Areas of coagulative type necrosis, crush artifact and lymphovascular invasion were also present. Mitotic figures were abundant and easily detected. Surface urothelium was regular and flat with no evidence of neoplasia (Fig. 1). Nuclei varied in size from 2 to 4 times the size of a small mature lymphocyte. Chromatin was finely granular. Open vesicular chromatin and conspicuous nucleoli were absent. Nuclear contour was frequently angulated and nuclear molding was prominent and well visible in some areas (Fig. 3). PAS and PAS-Diastase failed to reveal any amount of glycogen or mucin. All of the following Immunohistochemical stains were negative: Leukocyte common antigen (LCA), Vimentin, CD99, CD117 (c-kit), S-100, CEA, Cytokeratin 20, Cytokeratin 7, and High molecular weight cytokeratin (Clone 34ßE12).

Synaptophysin was diffusely positive in both cases (Fig. 4). Chromogranin A was negative in Case 1 and expressed in Case 2 (Fig. 5). Table I shows the antibodies used, the source, their clones and the working concentration.
FIGURE 4. Positive anti-synaptophysin immunohistochemical stain. Case 1 (400x).

FIGURE 5. Positive anti-chromogranin A immunohistochemical stain. Case 2 (400x).

TABLE I

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Source</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>CD117</td>
<td>T595</td>
<td>Biogenex™</td>
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</tr>
<tr>
<td>CD99</td>
<td>H036.6</td>
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<tr>
<td>CEA</td>
<td>Monoclonal BOL-94-11M-P</td>
<td>Biogenex™</td>
<td>Pre-diluted (Ready to use)</td>
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<tr>
<td>Chromogranin A</td>
<td>Monoclonal LK2H10</td>
<td>Biogenex™</td>
<td>Pre-diluted (Ready to use)</td>
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<td>Cytokeratin 20</td>
<td>IT-Ks 20.8</td>
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</tr>
<tr>
<td>S-100</td>
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<td>Synaptophysin</td>
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<tr>
<td>Vimentin</td>
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Immunohistochemistry was performed on deparaffinized sections by Standard Avidin-Biotin-Complex (ABC) Immunoperoxidase technique, with diaminobenzidine (DAB) as chromogen. When needed, antigen retrieval was performed by boiling the slides for 10 minutes in a citrate buffer solution 0.01M, pH 6.0 in a pressure cooker. Sections were counterstained with hematoxylin.

**DISCUSSION**

Clinical features

The first case of small cell carcinoma of the urinary bladder was reported in 1981 by Cramer et al. [1]. The epidemiology, risk factors and clinical presentations are similar to those of urothelial (Transitional cell) carcinoma, which is the most common malignancy of this organ [7]. The majority of patients are male (M/F ratio of 3.3:1), 36 to 85 years old, with a mean age at diagnosis of 66 years [2, 8]. A history of smoking is frequently present. Gross hematuria with or without dysuria is the most common clinical presentation [2]. Some patients present with irritative symptoms such as dysuria, nocturia, urgency, urinary obstructive symptoms or localized abdominal pain [2]. Non-specific signs and symptoms of malignancy such as anorexia and weight loss are frequent. Occasionally, the patients have a paraneoplastic syndrome such as hypercalcemia, hypophosphatemia, or ectopic secretion of adrenocorticotropic hormone (ACTH) [1, 9-12]. Table II shows the stage at presentation as reported in some studies.

### Table II - Stage at Diagnosis of Bladder Small Cell Carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Stage I (T,Nx,Mx)*</th>
<th>Stage II (T,Nx,Mx)*</th>
<th>Stage III (T,Nx,Mx)*</th>
<th>Stage IV (T4b, N1 or N2, M0, M1)</th>
<th>Stage Unknown</th>
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<td>Bastus [33]</td>
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</tr>
</tbody>
</table>

* The N and M parameters were not specified in the study.
* Patients with limited disease (LD) are all those with a stage of any TN0M0 or any TN1M0.
* Patients with extensive disease (ED) had a stage of T1N0M0, T2N0M0 or T3N0M0.
** Five patients were staged as D1 (Jewett-Strong-Marshall) system. It is not clear how many of these cases would be classified as T4a (Stage III) or T4b (Stage IV) in the AJCC 2002 Bladder Cancer Staging System.

Pathology and differential diagnosis

Grossly, small cell carcinoma of the bladder most commonly presents as a large solid polyoid mass but it may also appear as ulcerated plaque like lesion [13].

Histologically, it is identical to small cell carcinoma of the lung [4, 13-14]. Vascular invasion is almost always present and invasion of the Muscularis propria is very common at presentation [13]. There is often a second type of carcinoma that is intimately admixed with it (Urothelial carcinoma,
squamous cell carcinoma, adenocarcinoma). The pure form is encountered in 12% to 61% of cases [2-3, 11, 13].

Differential diagnosis includes mainly lymphoma [15-16], plasmacytoid urothelial carcinoma [17-19], poorly differentiated high grade urothelial carcinoma, invasion by prostatic small cell carcinoma, pulmonary small cell carcinoma with bladder metastases and the extremely rare primary primitive neuroectodermal tumor (PNET) [20].

The cytological and histological features remain the gold standard for the diagnosis (as in pulmonary small cell carcinoma). Immunohistochemistry is an adjunct and the immunoprofile has to be interpreted with caution and in light of the morphological features, otherwise it can be misleading rather than helpful.

Pulmonary small cell carcinoma metastatic to the urinary bladder is indistinguishable from primary small cell carcinoma by morphology and immunohistochemistry [21-23]. Clinical history and the presence of associated urothelial carcinoma, squamous cell carcinoma or adenocarcinoma are much more helpful.

Small cell carcinoma of the prostate can occasionally invade the bladder. Its morphology and immunoprofile are almost identical to its urinary counterpart [24]. The presence of an admixed regular type prostatic adenocarcinoma in 43% of cases as well as the clinical and radiological features are helpful in reaching the correct diagnosis [24].

Primary primitive neuroectodermal tumor (PNET) of the urinary bladder is extremely rare [20]. It is glycogen rich, strongly expresses CD99 (MIC2 gene product) and Vimentin and it is usually negative for Synaptophysin and Chromogranin [20].

Treatment

The optimal treatment strategy for this type of tumor remains unknown and is still controversial [7]. Its scarcity precludes prospective randomized studies. It took 20 years for a single center to include 25 patients in a prospective study [5]. In another series, only four cases were diagnosed during a 19-year period [25]. All the currently available data indicate that surgery alone (TUR or cystectomy) is not an optimal therapy [26]. The majority of patients present with metastatic disease. Metastases rather than loco-regional tumor progression are the usual cause of death [5, 25]. Metastases involve the regional lymph nodes, lung, liver, bone and brain [2, 13, 27]. Table III summarizes the treatment modalities and outcome as reported in some of the studies cited in this article.

Even in the setting of clinically localized and surgically resectable disease, many patients die within one year of diagnosis, which indicates that these tumors have a high metastatic potential and that a significant number of patients with presumed (apparent) localized disease have already undiagnosed micro metastases at presentation [8, 28]. Treatment strategies incorporate multimodality therapy such as cystectomy and radiation therapy [28] or incorporation of chemotherapy with local therapy such as cytectomy [29-31] and combination of chemotherapy and radiation therapy [32-33].

The high growth rate had led sometimes to the abor tion of a planned cystectomy and adjuvant chemotherapy, due to the discovery – at the time of surgery – of unresectable tumor (i.e., higher stage than what was expected based on preoperative clinical staging) [27]. It is not clear however whether this phenomenon reflected clinical understaging or rapid growth rate [27]. Sieffer-Radtk et al. from M.D. Anderson Cancer Center found that even in the presence of potentially resectable tumor by radical cystectomy, pre-operative chemotherapy offered better 5-year survival rate than initial cystectomy followed by chemotherapy (78% vs. 36%). In their study, preoperative chemotherapy often resulted in pathologica l down staging while the opposite occurred in cases treated by initial cystectomy. The authors concluded that surgery was still needed after chemotherapy because residual tumor is often present [27].

The similarity between small cell carcinoma of the lung and small cell carcinoma of the urinary bladder in terms of pathology, high growth rate, advanced stage at presentation, frequent subclinical metastases and chemosensitivity, as well as the scarcity of small cell carcinoma of the bladder, prompted some authors to approach it the same way as its pulmonary counterpart (which is much more frequent and better studied), i.e. as a systemic disease from the onset, with no role for surgery [5, 32]. A combination of chemotherapy and radiotherapy – depending on the extent of the disease – was recommended (organ sparing treatment strategy) [5]. The authors suggested a two-tier staging system similar to the one used in small cell carcinoma of the lung (i.e. limited disease and extensive disease). Those with limited disease are defined as those whose disease could be included within a radiation field [34] (i.e. disease limited to the pelvis, no distant metastases and involvement of maximally one loco-regional lymph node less than 2 cm) [5, 32]. Otherwise, the disease is considered to be extensive. The rationale for adding radiotherapy to systemic therapy is the small but significant documented improvement in overall survival in cases of lung small cell carcinoma [34-35]. Bex et al. [5] concluded that bladder preserving surgery (chemotherapy and radiotherapy) is an attractive and feasible therapeutic option. However, the high prevalence of elderly patients with co-morbidities precludes chemoradiotherapy in a significant portion (more than half the patients with limited disease in their study).

Chemotherapy with a neuroendocrine regimen containing etoposide and cisplatin (E/P) or ifosfamide and doxorubicin was more likely to successfully eradicate the small cell component compared with regimens typically used for urothelial carcinoma [27]. Cisplatin chemotherapy in particular was associated with a favorable prognosis [4, 8, 30, 36]. The possibility that the good performance status (required for cisplatin-based chemotherapy) is mainly responsible for the improved survival was raised however [5].
**TABLE III • REPORTED TREATMENT MODALITIES AND OUTCOME IN BLADDER SMALL CELL CARCINOMA**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Treatment Modalities</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Cheng [2]      | 64                 | - SURG  
- SURG + CH + RT  
- CH + RT                                                | 1 year disease free survivals for combined SURG + CH + RT and CH + RT: 57% and 55% respectively (Non significant difference)  
5 year disease free survivals for combined SURG + CH + RT and CH + RT: 16% and 18% respectively (Non significant difference) |
| Abrahams [3]   | 29                 | - TUR : 2 (both stage I)  
- CH + SURG : 9  
- SURG : 9  
- CH : 9 with initial metastases                          | Median overall survival for all patients: 23 months                      
40% survival at 5 years                                        |
| Blomjous [4]   | 18                 | - SURG : 1  
- TUR + SURG : 2  
- TUR + RT : 9  
- TUR + RT + CH : 2  
- TUR + CH : 1  
- SURG + CH : 1  
- CH + SURG : 1  
- No treatment : 1                                             | 14 patients died of tumor at 1 to 15 months of follow-up (median, 7 months)  
Of the 5 patients who received chemotherapy, 3 were still alive at 22, 23, and 58 months of follow-up  
The 2 remaining patients who had chemotherapy died after a prolonged interval of 15 months  
Only one patient treated with cystectomy was free of recurrent tumor after 5 years |
| Bex [5]        | 25                 | - CH : 10  
- CH + RT : 8  
- Complete TUR + RT : 5  
- SURG : 2                                                   | The difference in survival of the patients who received chemotherapy versus those who did not was significant regardless of tumor stage (15 months vs. 4 months) |
- Partial cystectomy : 4  
- TUR : 1  
- CH + SURG : 1  
- SUR + CH : 12  
- RT + SURG : 2  
- RT + SUR + CH : 1  
- CH : 5  
- No treatment : 1                                             | Overall median survival of 1.7 years  
Six out of the 12 patients with Stage II disease were alive and disease free. They had radical cystectomy. The 3 patients who had partial cystectomy developed local recurrence and metastases  
Only 2 of stage III patients (total of 13) were alive and disease free. They had radical cystectomy with adjuvant chemotherapy.  
All Stage IV patients who presented with distant metastases (M1) (5 patients) and received chemotherapy died within 4 months  
Only 2 of stage IV patients who presented with pelvic lymph nodes metastases (N1 or N2, M0) (total of 13 patients) were alive at 6.7 years and 7.6 years. Both were treated with adjuvant chemotherapy |
| Soriano [22]   | 10                 | - SURG + CH + RT : 3  
- SURG + CH : 3  
- TUR only : 3  
- TUR + RT : 1                                                | With SURG + CH + RT the survivals were 12, 15 and 16 months (mean 14)  
Two patients treated with SURG and CH were alive at the last follow-up at 16 months. The third one was lost for follow-up  
With TUR only, survival was 2-5 months  
The patient treated with TUR and RT died after 6 months |
| Trias [26]     | 23                 | - TUR : 7  
- TUR + CH : 6  
- TUR + RT : 3  
- TUR + CH + RT : 1  
- SURG : 4  
- SURG + CH : 1  
- Partial cystectomy : 1                                     | 18 patients died within 32 months (82% mortality rate)  
One patient (Stage II, TUR + RT) was living with disease (Bone metastasis) at 42 months  
Three patients were alive with no disease at 36 and 48 months (TUR + CH) and at 60 months (TUR only)  
One patient was lost for follow-up |
| Sieker-Radtke [27] | 46              | - SURG : 25 (7 of which underwent postoperative chemotherapy)  
- CH + SURG (Neoadjuvant CH) : 21                           | Initial cystectomy: 36% disease specific survival at 5 years  
Preoperative chemotherapy: 78% disease specific survival at 5 years, with no cancer related deaths observed beyond 2 years and 4 cancer related death. |
Potential role for targeted therapy

CD117 (c-kit) is a type III transmembrane tyrosine kinase growth factor receptor. Gain of function mutation (Activation mutation) of the receptor occurs in a large subset of gastrointestinal stromal tumors (GIST), leading to constitutive (permanent) phosphorylation and activation of the receptor, regardless of the presence of the ligand.

Pan et al. [37] showed positive immunostaining for c-kit in 14 of 52 cases (27%) of small cell carcinoma of the bladder.

Epidermal growth factor receptor (EGFR ; HER-1 ; ERB-B1) and EGFR-2 (HER-2 ; ERB-B2) are transmembrane tyrosine kinase growth factor receptors, which are over expressed in many malignancies. Abrahams et al. [3] demonstrated expression of EGFR in 4 of 11 cases (36%) of small cell carcinoma of the bladder by immunohistochemistry.

Soriano et al. [22] observed typical membranous staining indicating over expression of EGFR-2 in 5 of 10 cases (50%) of small cell carcinoma of the bladder.

These data raise the question of whether therapy against these target molecules might prove beneficial in patient management.

The successful treatment of some GIST tumors by imatinib mesylate (Gleevec®), which is an inhibitor of c-kit, raises the question of whether treatment against these target molecules (targeted therapy) might be beneficial in the case of small cell carcinoma of the bladder.

Additional studies are needed however, especially regarding the status of the c-kit receptor. The large data obtained from the study of gastrointestinal stromal tumors (GISTs) indicate that the expression of the c-kit antigen – as detected by immunohistochemistry – can be associated with either the wild type or the mutated form of the receptor [38]. The responsiveness of GIST to imatinib mesylate is variable, depending on the presence or absence of gain of function mutation and depending on the mutated exon [39-41].

### Study Details

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Treatment Modalities</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmg [28]</td>
<td>22</td>
<td>– TUR + RT : 16&lt;br&gt;– Preoperative RT + SURG : 1&lt;br&gt;– SURG : 1&lt;br&gt;– CH : 2&lt;br&gt;– 2 patients died soon after diagnosis and received no treatment</td>
<td>– Of the 18 patients who had loco-regional therapy, 13 (72%) died of disease after 0.5 to 19 months (median 7.3) and 5 had no evidence of disease after a median observation of 10 years (6-10y)&lt;br&gt;– The patients who received CH only, survived for 7 and 15 months</td>
</tr>
</tbody>
</table>
| Grignon [30]  | 22                 | – SURG + CH (Adjuvant CH) : 5<br>– Partial cystectomy + CH : 1<br>– RT + CH : 1<br>– SURG : 1<br>– Partial cystectomy : 4<br>– RT only : 2<br>– CH only : 2<br>– No treatment : 2 | – Of the 5 patients treated with a combination of surgical resection and systemic multidrug chemotherapy (all stages), 4 were alive and disease-free at 10, 14, 28, and 51 months, whereas the fifth was also alive, but with progressive disease at 36 months.  
  – Statistically significant differences in outcome were not evident, given the low number of cases |
| Oesterling [31]| 2                  | – SURG + CH                                                                            | Both patients were disease free at 1 and 2.5 years later |
| Lohrisch [32] | 10                 | – Tumor debulking by complete TUR + CH + RT : 9<br>– SURG + CH + RT : 1                | Overall survival at 2 years and 5 years : 70% and 44% respectively.  
  – Disease free survival at 2 and 5 years : 70%.  
  – Mean and median overall survival : 47 months and 41 months respectively |
| Bastus [33]   | 5                  | – CH + RT : 3<br>– CH + RT followed by SURG : 1 (because of local recurrence)<br>– CH + SURG : 1 | – The four patients treated with initial chemotherapy followed by radiotherapy were alive and free of disease after a follow-up period ranging between 27 months and 60 months.  
  – The patient treated with chemotherapy followed by radical cystectomy died of disease after 10 months |
| Christopher [36]| 5                 | – TUR : 1<br>– Partial cystectomy : 1<br>– SURG : 1<br>– RT : 1<br>– RT + CH : 1 | – Two patients were alive with no evidence of disease at 12 months and 11 years (TUR and Partial cystectomy cases respectively)<br>– The three remaining patients died of metastatic disease after 8 to 32 months |

SURG : Radical cystectomy  
RT : External beamradiotherapy  
CH : Chemotherapy  
TUR : Trans urethral resection
CONCLUSION

Small cell neuroendocrine carcinoma of the bladder is a rare but highly aggressive neoplasm that almost always presents at an advanced stage. As in urothelial (transitional cell) carcinoma, smoking is the major risk factor. Signs and symptoms are not specific. Histologically, it might be confused with poorly differentiated high grade urothelial carcinoma and lymphoma. It is important to distinguish it from these latter entities, as the treatment and prognosis are completely different. There is still no universal agreement regarding the ideal therapeutic approach, given the scarcity of the cases and lack of large prospective randomized studies. As in its pulmonary counterpart, death is mainly due to metastatic disease rather than locoregional recurrence. Neoadjuvant or adjuvant cisplatin-based chemotherapy regimens appear to provide a survival advantage. The need for local therapy and its choice (Surgery vs. Radiotherapy) is a more controversial issue. The expression of the tyrosine kinase growth factor receptor c-kit (CD117) by the neoplastic cells raises the question of whether targeted therapy would be beneficial. Studies that investigate the presence or absence of gain of function mutation of the c-kit receptor and its prevalence in small cell carcinoma of the bladder are needed.

REFERENCES

26. Trias I, Alcaba F, Condom E et al. Small cell carcinoma of the urinary bladder. Presentation of 23 cases and


