

## Small Cell Carcinoma of the Bladder

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**E**xtrapulmonary small cell (oat cell) carcinoma has been reported in the head and neck, pancreas, breast, thymus, skin, and gastrointestinal system.<sup>1-8</sup> Small cell carcinoma of the bladder, however, is exceedingly rare. Fewer than 100 cases of small cell carcinoma of the bladder have been reported in the medical literature, comprising less than 1% of all bladder tumors.<sup>9-16</sup> Small cell carcinoma tumors in the bladder usually have an aggressive clinical course, often presenting with metastases at the time of diagnosis. Although most clinicians believe the optimal treatment for small cell carcinoma of the bladder is a combination of surgical resection and adjuvant chemotherapy, appropriate therapy is uncertain because the information regarding these tumors is limited. This article presents a case of small cell carcinoma of the bladder in a 53-year-old man. Treatment options as well as adjuvant therapy are discussed.

### CASE PRESENTATION

A 53-year-old man presents to the emergency department with acute onset of painless gross hematuria. The patient's medical history is significant for diverticulitis, alcoholic pancreatitis, and a 60 pack-year smoking history.

### Physical and Laboratory Evaluations and Hospital Admission

Physical examination is unremarkable. No signs of lymphadenopathy or palpable abdominal, scrotal, or inguinal masses are evident. Laboratory tests and standard radiography of the abdomen are normal. Chest radiography is performed to rule out a primary lung lesion and yields normal results.

The patient is admitted to the hospital. Intravenous pyelography demonstrates bladder outlet obstruction (**Figure 1**). The gross hematuria is treated with bladder irrigation and drainage via a three-way Foley catheter. Cystoscopy reveals a 7-cm sessile tumor that extends into

the bladder neck region of the prostate. Transurethral biopsy demonstrates undifferentiated small cell carcinoma of the bladder with invasion into the bladder's muscular layer (**Figures 2 and 3**). Immunoperoxidase stains (**Figures 4-6**) reveal tumor cell reactivity to cytokeratin, neuron-specific enolase, and chromogranin and confirms the diagnosis of small cell carcinoma. Computed tomography scans of the abdomen and pelvis do not demonstrate regional adenopathy or metastasis. Based on these findings, the patient's cancer is staged at T2 with no lymph node invasion or distant extension (T2N0M0) (**Table 1**).

### Surgical Exploration, Treatment, and Outcome

Surgical exploration reveals a large mass in the bladder with local extension into the pelvis. An enlarged pelvic lymph node and two liver nodules are also discovered. Biopsy demonstrates a normal lymph node and two foci of metastatic small cell carcinoma without evidence of neuroendocrine differentiation. Because the patient is now at clinical stage T4bN1M1, radical cystectomy is not performed. The patient is discharged home and treated with four cycles of chemotherapy (cisplatin [80 mg/m<sup>2</sup> intravenous bolus] and etoposide [100 mg/m<sup>2</sup>/day for 3 days]) on an outpatient basis. Four months after presentation, the patient dies because of septic complications related to chemotherapy.

### DISCUSSION

#### Epidemiology

Since the first case of small cell carcinoma of the bladder was reported in 1981, most patients diagnosed

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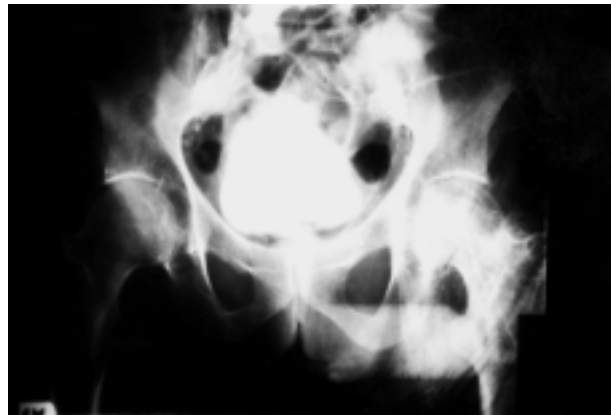
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with this rare disease have been male (male to female ratio, 7.6 to 1) between ages 60 and 80 years.<sup>9,12,17</sup> Like the patient in this case study, most patients who present with small cell carcinoma of the lung or other extrapulmonary sites usually have an extensive smoking history.<sup>13-15,18</sup> However, most patients with small cell carcinoma of the bladder are not tobacco users. Whether tobacco has a causative effect on disease progression is unclear because of the paucity of information on small cell carcinoma of the bladder. Patients often have a history of painless gross hematuria; however, their physical examination is usually unremarkable.

### Pathogenesis

The origin of small cell carcinoma of the bladder is unknown. The majority of small cell carcinomas of the bladder have associated histologic patterns, including transitional cell carcinoma, squamous carcinoma, or spindle cell carcinoma.<sup>19</sup> Recent cytogenetic studies on patients with small cell carcinoma of the bladder have demonstrated that the tumors had rearrangement of the long arms of chromosomes 6, 9, 11, 13, and 18, with hypertriploid DNA and p53 expression.<sup>20</sup> Immunohistochemical studies have revealed neurosecretory granules in most small cell carcinoma of the bladder tumors, a fact that leads many investigators to postulate that the tumors derive from the neuroendocrine amine precursor uptake and decarboxylation cells.<sup>21</sup> However, other reports suggest a multipotential stem cell origin, which would account for the minor component of admixed non-small cell carcinoma commonly seen in these tumors.<sup>9,15,16</sup> Occasionally, small cell carcinoma of the bladder has demonstrated ectopic hormone production.<sup>22</sup> In one report, histopathologic analysis demonstrated hyperphosphatemia without hypercalcemia before tumor resection, suggesting that humoral production disturbed phosphate metabolism. The phosphate level returned to normal levels after surgical resection.<sup>10</sup> Other reported cases of small cell carcinoma of the bladder have been associated with hypercalcemia, which was attributed to skeletal metastasis.<sup>14</sup>

Small cell carcinoma of the bladder can occur at any location in the bladder mucosa, but is usually located on the bladder's lateral walls. These tumors tend to be broadly based and polypoid, measuring between 2 and 10 cm in diameter, and are commonly ulcerated and hemorrhagic.<sup>12</sup> Local invasion through the bladder wall is common and metastatic sites mimic transitional cell carcinoma (ie, parailiac and paraortic lymph nodes, liver, vertebral and costal bones, abdominal cavity).



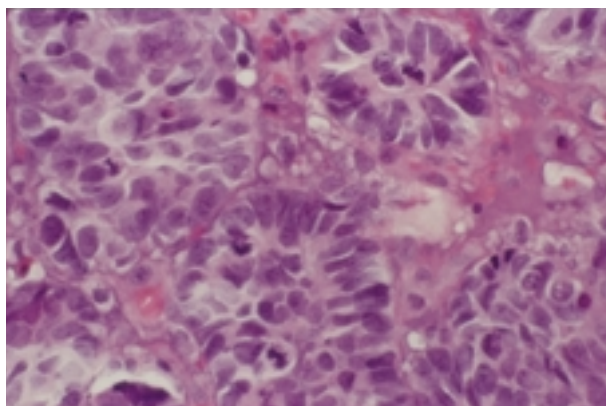
**Figure 1.** Intravenous pyelography demonstrates the trabeculated wall of the urinary bladder with outlet obstruction.

### Diagnosis

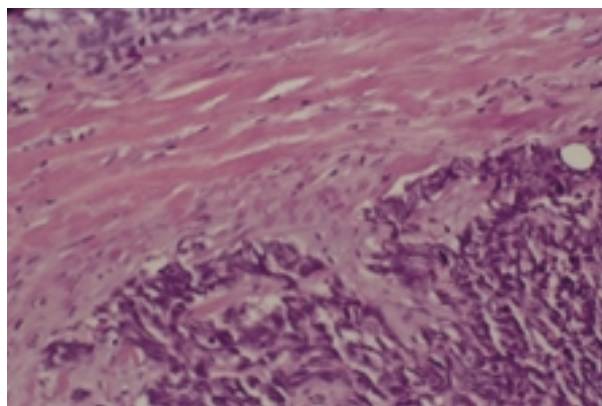
Diagnosis of small cell carcinoma of the urinary bladder is most often accomplished via cystoscopy and transurethral biopsy. The specific characteristics of small cell carcinoma are then confirmed by light microscopy and immunohistochemical staining. The microscopic appearance of small cell carcinoma is similar to undifferentiated small cell carcinoma of the lung. Tumors are composed of solid sheets of small cells with hyperchromatic nuclei and scant cytoplasm, as evidenced by the patient in this case study. Admixed non-small cell carcinoma comprises 5% to 15% of the histologic specimen,<sup>8,12</sup> and focal necrosis and a moderate mitotic rate are common. In cases for which light microscopy is not definitive, immunocytochemical staining for epithelial markers (eg, cytokeratin, epithelial membrane antigen, cell adhesion molecule 5.2) rather than panlymphoid markers (eg, leukocyte common antigen) are helpful to rule out lymphoreticular neoplasm.<sup>17</sup> Further distinction can be made with immunocytochemical stains for neuroendocrine antigens (eg, neuron-specific enolase, chromogranin A).<sup>10</sup> Most small cell carcinoma tumors of the bladder stain with at least one epithelial marker and two or more neuroendocrine markers, as demonstrated by the patient in this case study. However, cases without positive stains for any of these immunocytochemical markers have also been reported.<sup>18</sup>

### Therapy

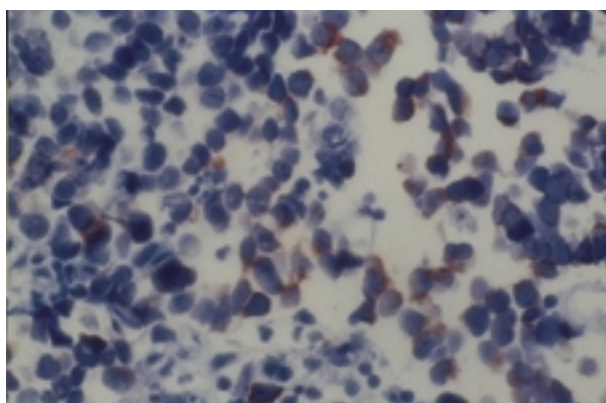
Recent reports suggest that the best treatment protocol for small cell carcinoma of the bladder includes aggressive surgical resection with adjuvant multi-drug systemic chemotherapy, especially in early-stage tumors.<sup>10,11</sup> Conversely, anecdotal reports have noted long-term survival in patients with small cell carcinoma



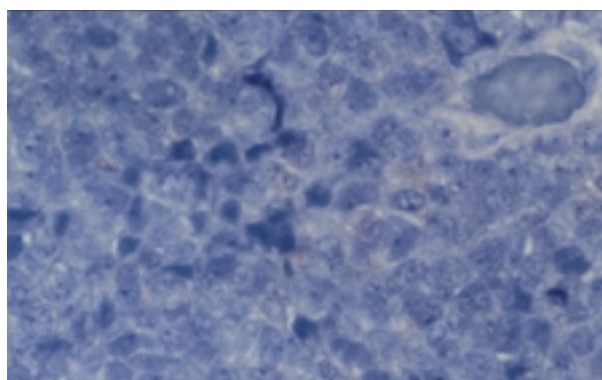
**Figure 2.** Histologic examination of the patient's transurethral biopsy demonstrates solid sheets of undifferentiated small cells with a moderate mitotic rate. Hematoxylin and eosin stain, X 40.



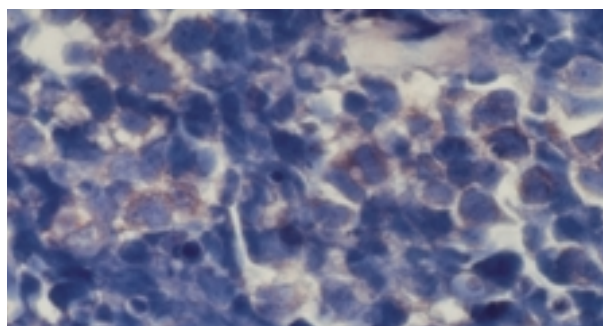
**Figure 3.** Histologic examination of the patient's transurethral biopsy demonstrates the small cell carcinoma invading the underlying muscular layer of the bladder. Hematoxylin and eosin stain, X 20.



**Figure 4.** Histologic examination reveals paranuclear dot staining (brown areas) typical for cytokeratin. Immunoperoxidase stain, X 40.



**Figure 5.** Histologic examination shows diffuse cytoplasmic immunoreactivity (faint brown areas) in the tumor cells. Neuron-specific enolase immunoperoxidase stain, X 40.



**Figure 6.** Histologic examination reveals chromogranin (brown areas) in the tumor cells. Focal, intracytoplasmic, immunoperoxidase stain, X 40.

**Table 1.** American Cancer Society Staging for Urinary Bladder Carcinoma

Primary Tumor (T)	
<b>TX</b>	Primary tumor cannot be assessed
<b>T0</b>	No evidence of primary tumor
<b>Ta</b>	Noninvasive papillary carcinoma
<b>Tis</b>	Carcinoma in situ: "flat tumor"
<b>T1</b>	Tumor invades subepithelial connective tissue
<b>T2</b>	Tumor invades superficial muscle (inner half)
<b>T3</b>	Tumor invades deep muscle (outer half) or perivesical fat
<b>T3a</b>	Tumor invades deep muscle (outer half)
<b>T3b</b>	Tumor invades perivesical fat
	i. Tumor invades perivesical fat microscopically
	ii. Tumor invades perivesical fat macroscopically (extravesical mass)
<b>T4</b>	Tumor invades any of the following: prostate, uterus, vagina, pelvic or abdominal wall
<b>T4a</b>	Tumor invades any of the following: prostate, uterus, vagina
<b>T4b</b>	Tumor invades pelvic or abdominal wall
Regional Lymph Nodes (N)	
Regional lymph nodes are lymph nodes within the true pelvis; all other lymph nodes are distant nodes.	
<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in a single lymph node, 2 cm or less in greatest dimension
<b>N2</b>	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
<b>N3</b>	Metastasis in a lymph node more than 5 cm in greatest dimension
Distant Metastasis (M)	
<b>MX</b>	Presence of distant metastasis cannot be assessed
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis

Adapted with permission from Murphy GP, Lawrence W Jr, Lenhard RE Jr: *American Cancer Society Textbook of Clinical Oncology*, 2nd ed. Atlanta, GA: American Cancer Society, 1995:319.

of the bladder treated primarily with chemotherapy.<sup>13,23</sup> External beam radiation following chemotherapy may also be helpful in select cases.<sup>24</sup> However, the overall prognosis still remains poor in most patients, especially in patients with local invasion and distant metastasis. For example, in a recent study, 14 of 18 patients with small cell carcinoma of the bladder died within 9.5 months of diagnosis.<sup>12</sup>

#### SUMMARY

In conclusion, extrapulmonary small cell carcinoma has been reported to occur in a variety of organs but is seldom encountered in the urinary bladder. Diagnosis is usually made by light microscopy, but may require specialized immunohistochemical staining. The tumor has a strong propensity to metastasize; thus, most patients present in advanced stages and undergo a rapidly fatal course. If clinically feasible, extensive surgical resection in combination with adjuvant multidrug systemic chemotherapy provides the only chance for potential long-term survival. **HP**

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