Scientific Research Publishing

Journal of Cancer Therapy, 2026, 17(1), 6-12
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Metastatic Small Cell Neuroendocrine Carcinoma of the Bladder: Case Report and Literature Review

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How to cite this paper: Oufrid, A., Aabboub, B., Amaadour, L., Oualla, K., Benbrahim, Z., Arifi, S. and Mellas, N. (2026) Metastatic Small Cell Neuroendocrine Carcinoma of the Bladder: Case Report and Literature Review. *Journal of Cancer Therapy*, **17**, 6-12.
https://doi.org/10.4236/jct.2026.171002

Received: December 5, 2025
Accepted: December 27, 2025
Published: December 30, 2025

Abstract

Background: Small cell neuroendocrine carcinoma of the bladder (SCNECB) is a rare entity, accounting for less than 1% of bladder tumors. It progresses rapidly and has a poor prognosis. **Case Presentation:** We report the case of a 62-year-old man, a chronic smoker, admitted for gross hematuria that had been developing for a month. An abdominal-pelvic CT scan revealed an infiltrating bladder mass associated with liver metastases. RTUV confirmed the diagnosis of small cell neuroendocrine carcinoma through immunohistochemistry: chromogranin A, synaptophysin, and CD56 positive, Ki-67 at 80%. The patient received six cycles of cisplatin-etoposide, with an initial partial response. The disease then progressed rapidly, leading to the patient's death eight months after diagnosis. **Conclusion:** This case illustrates the early metastatic presentation and rapid progression of small cell neuroendocrine carcinoma of the bladder. Despite platinum-based chemotherapy, the prognosis remains poor, especially in resource-limited countries.

Keywords

Bladder, Neuroendocrine Carcinoma, Small Cell, Metastases, Chemotherapy

1. Introduction

Small-cell neuroendocrine carcinoma of the bladder (SCNEC-B) is a rare and highly aggressive tumor, accounting for less than 1% of all bladder cancers [1]. Patients generally present at an advanced stage, with symptoms dominated by hematuria, reported in nearly 90% of cases in several clinical series [1] [2]. Typical histopathological features include small basophilic cells, scant cytoplasm, very

high mitotic activity, and areas of tumor necrosis. Immunohistochemistry plays a central role in the diagnosis, confirming neuroendocrine differentiation through the expression of chromogranin A, synaptophysin, and CD56 [2]. The Ki-67 proliferation index is usually very high, reflecting the biological aggressiveness of this tumor.

From a prognostic standpoint, several studies have demonstrated an especially poor outcome. Analysis of the U.S. SEER database reports a median overall survival of approximately 11 months across all stages, highlighting the rapid progression of this cancer [3]. In most institutional series, patients present with muscle-invasive or advanced disease at diagnosis [1] [4], and distant metastases—particularly hepatic, osseous, or nodal—are frequently observed.

In the absence of specific guidelines and given the rarity of this entity, management relies primarily on platinum-based chemotherapy, which is the most commonly used approach in locally advanced or metastatic stages [4]. Despite variable initial sensitivity, overall survival remains limited.

We report here a case of small-cell neuroendocrine carcinoma of the bladder, diagnosed at a metastatic stage from the outset, illustrating the diagnostic and therapeutic challenges encountered in our setting.

2. Case Presentation

2.1. Demographic Data and Medical History

A 62-year-old man, with no significant past medical history, chronic smoker, and without known occupational exposure to carcinogens, presented with hematuria.

2.2. Initial Symptoms

The patient reported macroscopic hematuria evolving for one month, with no associated symptoms. His general condition was preserved (ECOG 1).

2.3. Laboratory Tests

Initial laboratory workup showed:

- Hemoglobin: 11.2 g/dL.
- Creatinine: 11 mg/L.
- Creatinine clearance ≥ 60 mL/min.
- The lactate dehydrogenase (LDH) level was moderately elevated at 420 IU/L, corresponding to approximately 1.7 times the upper limit of normal.

2.4. Imaging

Abdominopelvic CT scan revealed:

- A 4-cm infiltrating bladder mass.
- Pelvic lymphadenopathy (up to 18 mm).
- Multiple bilobar liver metastases (up to 22 mm).
- Bone metastases.

The findings were consistent with de novo metastatic stage IV disease.

2.5. TURBT and Histology

Cystoscopy showed a 4 - 5 cm exophytic bladder tumor. An incomplete transurethral resection of the bladder tumor (TURBT) was performed due to extensive tumor involvement and deep invasion of the bladder wall, which prevented safe complete resection.

Histology revealed:

- Small round cells with scant cytoplasm and hyperchromatic nuclei
- Numerous mitotic figures and extensive necrosis

Immunohistochemistry was positive for:

- Synaptophysin
- Chromogranin A
- CD56, with a Ki-67 index of 80%

The diagnosis of small-cell neuroendocrine carcinoma of the bladder was confirmed.

2.6. Therapeutic Management

Following multidisciplinary tumor board discussion, the patient received palliative platinum-based chemotherapy:

- Cisplatin 75 mg/m^2 on Day 1.
- Etoposide 100 mg/m^2 on Days 1 – 3.

The regimen was repeated every 3 weeks.

The patient completed 6 cycles, well tolerated overall, except for grade 2 neutropenia managed with secondary prophylaxis using G-CSF.

2.7. Clinical Course

- **After 3 cycles:** Intermediate partial response with significant reduction of the bladder tumor and liver metastases.
- **After 6 cycles:** Sustained partial response, with disappearance of some liver lesions and persistence of small residual nodules.

Clinically, hematuria resolved and dysuria markedly improved.

However, within weeks after completing treatment, the patient's general condition progressively deteriorated to ECOG 3, requiring exclusively palliative care. Second-line chemotherapy could not be initiated.

The patient died, with an overall survival of 8 months from diagnosis.

3. Discussion

Small-cell neuroendocrine carcinoma of the bladder is an exceptional entity, but its aggressiveness makes it a major diagnostic and therapeutic challenge. This case illustrates several features commonly described in the literature: occurrence in an older male, chronic smoking, presentation with hematuria, de novo metastatic disease, and rapid progression despite appropriate chemotherapy. Analysis of our case, placed in the context of current evidence, highlights the key issues surrounding this rare tumor.

3.1. Demographic Profile and Risk Factors

SCNEC of the bladder predominantly affects older men, with a mean age at diagnosis of about 67 years according to a clinical study of 51 patients [5]. Smoking is strongly associated with its development, reported in more than 50% of published cases [6].

Our patient (62 years old, heavy smoker) therefore fits the classical epidemiological profile.

3.2. Clinical Presentation

Hematuria is the most common presenting symptom, observed in 67% - 100% of cases in the series by Grignon *et al.* [6].

Irritative or obstructive urinary symptoms may occur but are not constant. The frequent absence of systemic signs contributes to diagnostic delays [7].

The isolated macroscopic hematuria observed in our patient thus corresponds to the most typical clinical presentation.

3.3. Imaging and Stage at Diagnosis

SCNEC is characterized by early dissemination. In a study of 533 patients from the SEER registry, 35% already had metastatic disease at diagnosis, with a median survival of 12 months [8].

Liver metastases are among the most frequent sites, as also reported in a series of 15 metastatic patients from the Léon-Bérard Center [9].

The presence of liver metastases at diagnosis in our patient therefore aligns perfectly with this aggressive pattern.

3.4. Histological and Immunohistochemical Findings

Histologically, small hyperchromatic cells, numerous mitoses, and extensive necrosis are typical features of SCNEC. Immunohistochemistry confirms neuroendocrine differentiation through expression of synaptophysin, chromogranin A, and CD56 [5].

In an analysis of 81 cases, Wang *et al.* frequently reported Ki-67 > 70%, reflecting extreme tumor aggressiveness [10].

Our patient's Ki-67 of 80% is consistent with these findings.

3.5. Differential Diagnosis for Small Cell Neuroendocrine Carcinoma of the Bladder

The differential diagnosis of small cell neuroendocrine carcinoma of the bladder includes high-grade urothelial carcinoma with neuroendocrine differentiation and metastatic small cell carcinoma from extra-vesical sites, particularly the lung. The predominance of neuroendocrine morphology, diffuse expression of neuroendocrine markers, and a high proliferation index support a diagnosis of primary small cell neuroendocrine carcinoma of the bladder. The absence of lung lesions on staging studies excludes a secondary origin.

3.6. Updated Literature Review

The literature review has been updated to include recent data from systematic reviews and large database analyses published since 2018. These studies confirm the aggressive nature of SCNECB, with most patients diagnosed at an advanced or metastatic stage. Median overall survival remains very limited, often less than 12 months, despite an initial response to platinum-based chemotherapy. These data help contextualize our clinical observation within the current evidence and highlight the need for treatment strategies adapted to available resources.

3.7. Therapeutic Approach and Initial Response

In the absence of standardized guidelines, platinum-based chemotherapy (cisplatin or carboplatin) combined with etoposide is the most commonly used regimen, by analogy with small-cell lung carcinoma [11].

Initial response rates are often satisfactory, but relapses occur rapidly.

Our patient achieved a partial response after six cycles of cisplatin-etoposide, in line with results from published clinical series.

3.8. Prognosis and Therapeutic Limitations

SCNEC carries a particularly poor prognosis. In a 20-year retrospective study of 38 patients, median survival was 11.8 months, with 1-, 3-, and 5-year survival rates of 47%, 26%, and 14% respectively [12].

In metastatic or relapsed patients, survival decreases to about 7 - 8 months despite chemotherapy [9].

The 8-month survival observed in our patient, along with rapid functional decline preventing second-line treatment, is therefore consistent with the expected disease course.

3.9. Perspectives

The rarity of SCNEC necessitates multicenter studies and the creation of international registries to better understand its mechanisms, optimize therapeutic strategies, and evaluate new potential treatments. Recent therapeutic advances, including immune checkpoint inhibitors, are currently under investigation in high-grade neuroendocrine carcinomas. Their role in the treatment of small cell neuroendocrine carcinoma of the bladder remains to be defined, and their availability is limited in many clinical settings.

In resource-limited countries, the management of small cell neuroendocrine carcinoma of the bladder is constrained by limited access to specialized immunohistochemistry, second-line treatments, and adequate supportive care.

4. Conclusions

Small-cell neuroendocrine carcinoma of the bladder is a rare but extremely aggressive tumor, often diagnosed at an advanced stage and associated with limited survival. This case highlights the typical features of the disease: initial hematuria, early liver metastases, partial response to cisplatin-etoposide, but early relapse and

rapid clinical decline leading to death.

Improving knowledge of this entity requires case reporting, registry development, and collaboration among specialized centers.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

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