*Case Report*

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# Small Cell Carcinoma of the Urinary Bladder, a Rare and Aggressive Entity: A Case Report and Review of the Literature

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**Abstract**

Small cell carcinoma of the urinary bladder (SCBC) is a type of rare malignant tumor of the urinary tract. As it does not have specific symptoms and its epidemiological features are similar to transitional cell carcinoma of the bladder, it is often misdiagnosed. SCBC is highly aggressive, metastasizes very early and has a poor prognosis, and consequently, it has become a focus for urological surgeons and oncologists. An A 60-year-old smoker, man was admitted to our hospital with a 6-month history of right pelvic pain, multiples episodes of gross, painless, hematuria, dysuria, and extreme fatigue. Abdominal computed tomography showed a neoplasm of 6x3 cm on the left posteriolateral wall of the bladder. The initial diagnosis was of transitional cell carcinoma of the bladder and surgery was performed to remove the tumor. However, the subsequent pathological examination suggested that the tumor was a small cell carcinoma. Small cell carcinoma is a highly malignant disease, with a high mortality rate, and it rarely occurs in the bladder. Upon review of a large number of studies, SCBC was not found to present with specific symptoms, making the early diagnosis of the disease difficult, however, commonly occurring symptoms included dysuria, painless gross hematuria and urinary tract obstruction.

**Keywords**: Small Cell Carcinoma; Chemotherapy.

## Introduction

Small cell carcinoma is also known as oat cell carcinoma. The disease has a high degree of malignancy, is not well differentiated from other diseases and has a poor prognosis. Small cell carcinoma (SCC) is one of the histopathological subtypes that demonstrates aggressive clinical behavior and most commonly arises in the lung. Though rare, it can occur at extra pulmonary sites also, such as the gastrointestinal tract, salivary gland, uterine cervix, and urinary tract. Extra pulmonary SCC comprises 4% of all SCCs [1]. Its incidence in the bladder is reported to be 0.3-0.7% of all primary carcinomas of the urinary bladder [1]. SCCs of urinary bladder (SCCB) share histopathological and immunohistochemical features with their pulmonary counterpart. The prognosis is poor due to local or distant metastases, and usually the muscle of the bladder is invaded. Due to the low incidence of the SCBC, there are few clinical data-based prospective case control studies. Therefore, it is difficult to establish a useful guideline for application in the clinic. It is common that SCBC is misdiagnosed as another tumor type, and is it therefore necessary to accumulate more experience to determine the best treatment plan.

## Case Report

A 60-year-old smoker, man was admitted to our hospital with a 6-month history of right pelvic pain, multiples episodes of gross, painless, hematuria, dysuria, and extreme fatigue. There was no mass palpable in the pelvis area. Ultrasound (USG) and computed tomography (CT) scan showed left lateral wall mass with no perivesical or lymph node involvement (Figure 1). Cystoscopy showed a non-papillary tumor at the left side of the posterior wall. Transurethral resection of the bladder tumor (TURBT) was performed. Pathologic findings demonstrated superficial, high grade transitional cell carcinoma (TCC) with lamina propria and muscle not involved. Patient was non complaint with his follow up protocol. However, recurrent tumors were detected at the same location after 60 months' follow up. TURBT was done and pathologic examination showed muscle-invasive TCC. Repeat contrast enhanced computed tomography (CECT) scan showed left lateral wall enhancing mass 6 cm x 3 cm, with diffuse thickening of left posteriolateral bladder wall. CECT also showed nodes along left internal iliac vessels. We performed radical cystectomy with pelvic lymphadenectomy with ileal conduit (Figure 2). An extensive neoplasm was found on the left posterior wall of the bladder during the surgery. The neoplasm was cauliflower like in appearance, 6x6x7 cm in size and fragile. A pathological examination of the specimen revealed, on gross examination a fungating (polypoidal) mass. On light microscopy, a tumoral process comprising sheets of noncohesive small cells. Cells were round, and the mitotic count was high. Nuclear chromatin was finely granular and evenly distributed. Numerous cells were in apoptosis. The tumor invaded the muscle of the bladder wall. Out of 10 nodes retrieved one was positive and lymphovascular invasion was present. (pT3a n1). Immunohistochemistry showed that the tumor expressed synaptophysin and neuron-specific enolase (NSE). The patient was sent to oncologist who had planned for chemotherapy but patient was non complaint with chemotherapy protocol and died after 11 months of starting chemotherapy.

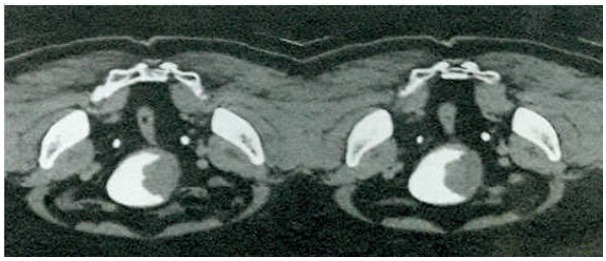

**Fig. 1:** A computed tomography (CT) scan of the pelvis showed a tumor at the left bladder wall

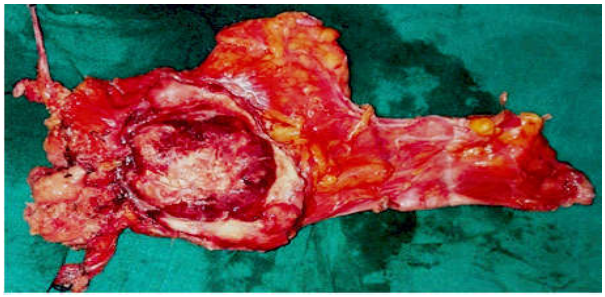

**Fig. 2:** Radical cystectomy specimen with large tumour obliterating nearly whole lumen

## Discussion

Bladder cancer is the second most common urologic malignancy. In the western countries, it is the fourth most common cancer in men and the eighth most common cancer in women [4]. Up to 95% of urinary bladder tumors are of epithelial origin, from which 90% are urothelial neoplasms [5]. Primary SCCB is a rare disease that accounts for less than 0.7% of all bladder cancers [1,2]. The disease was initially described in 1981 by Cramer *et al* [3]. Since then, 550 cases of SCCB have been diagnosed [6].

The diagnosis of SCCB is based on the criteria established by the WHO classification system, which are identical to those for small cell lung cancer (SCLC). Histological studies of SCCB showed sheets of uniformly small, round, mitotically active cells with overlapping nuclei and evenly distributed chromatin, lacking prominent nucleoli. Nuclear molding, tumor necrosis, and crush artifact were commonly seen [7]. Immunostaining analysis showed that cancerous cells expressed markers of neuroendocrine differentiation, including chromogranin, NSE (neural adhesion molecule) and synaptophysin [2,7,8,9]. In the majority of reported series, authors showed a higher incidence of mixed small cell carcinoma [6,10,11].

In the present case, the patient had mixed histology.

The mean age at diagnosis was 67.8 (20-91) years [13]. Painless gross hematuria was the most common presenting symptom in SCCB due to a large polypoid, ulcerated and deeply invasive tumor [10,11,12]. Dysuria and irritative symptoms had been reported as the second most common symptoms [7,12]. Urethral obstruction, weight loss, urinary tract infection, and ectopic ACTH secretion had been reported occasionally [7,12].

Diagnosis of SCCB was most often accomplished via cys-toscopy and transurethral biopsy. Immunocytochemi-cal staining is helpful if light

microscopy is not defini-tive [2,7,8,9]. A CT scan of the abdomen and pelvis, bone scan, and chest radiograph at the time of diagnosis of SCCB, and CT scan of the brain in the presence of neurologic signs or symptoms were warranted [13]. The sites of metastasis were the retroperitoneal lymph nodes, the liver, the lung, the bone, and the brain [6,10,12]. Metastasis from SCCB to the thyroid gland was reported [14]. For staging, Bex and Pan proposed to define both limited and extensive SCCB as analogous to small cell lung carcinoma[15,16].

Because SCCB is rare, and in the absence of randomized controlled trials, there is no standard treatment. SCCB tends to behave aggressively, with up to 25% of patients presenting metastatic disease and up to two-thirds developing distant recurrence. Chemotherapy plays a prominent role in the management of these tumors. In a multi-institutional review of 64 patients with a muscle invasive disease, a multivariate analysis indicated that neither chemotherapy, nor radiation, nor surgery had any impact on overall survival [11]. The poor prognosis of patients treated by radical cystoprostatectomy alone reported by Sved *et al* [13] supports the use of combination modality treatments. Nevertheless, in a multi-institutional retrospective study, patients with bladder transitional cell carcinoma and small cell carcinoma undergoing radical cystectomy share similar stage-specific clinical outcomes [17]. A retrospective study of 46 patients treated at the M. D. Anderson Cancer Centre has reported a 5-year survival of 78% for patients receiving neoadjuvant chemotherapy followed by cystectomy, versus 36% for patients undergoing cystectomy alone [10]. In the Mayo Clinic Study, the authors have proposed radical cystectomy for patients with locally advanced disease and adjuvant treatment for patients with stage III and VI (M0) disease [12]. Bastus *et al* . have reported on a series of five patients with locally advanced disease treated with sequential chemoradiotherapy. Four patients had long-term disease-free survival and overall survival [18]. Others authors expressed a realistic optimism and acknowledged a potential for long-term survival in patients with limited stage small cell cancer of the bladder treated with a combination of chemotherapy and sequential radiotherapy; the survival rate was 70% at 2 years and 44% at 5 years [19]. Theses results were recently confirmed by Bex *et al* . Median overall survival for the 17 patients treated by sequential chemoradiotherapy was equal to 32.5 months [20]. For stage IV disease, the chemotherapy remain the mainstay treatment. The M. D. Anderson Cancer Centre recommend the protocols used in the neuroendocrine tumors for both histological types: Pure small cell carcinoma and mixed small cell carcinoma of the bladder [10,21]. Other authors confirmed the efficacy of platinum-based chemotherapy [12,19,22].

The prognosis of SCCB is poor. The overall 5-year survival rate in all stages is 19% (16 to 25%) [11,12]. The pure small cell histology was shown to have poorer outcome than the mixed small cell histology [6,23].

## Conclusion

Primary SCCB is a very rare and aggressive tumor. In the absence of prospective study, the best treatment for this tumor cannot be established for certain. For localized disease, a combined treatment including surgery, chemotherapy, and radiotherapy, is necessary for achieving long-term disease-free and overall survival. For metastatic disease, the chemotherapy using a platinum agent is the mainstay treatment.

## References

1. Holmang S, Borghede G, Johansson SL. Primary small cell carcinoma of the bladder: A report of 25 cases. J Urol 1995;153:1820-2.
2. Blomjous CE, Vos W, De Voogt HJ, van der Valk P, Meijer CJ. Small cell carcinoma of the urinary bladder: A clinicopathologic, morphologic, immunohistochemical and ultrastructural study of 18 cases. Cancer 1989;64:1347-57.
3. Cramer SF, Aikawa M, Cebelin M. Neurosecretory granules in small cell invasive carcinoma of the urinary bladder. Cancer 1981;47:724-30.
4. Haresh KP, Julka PK, Sharma DN, Rath GK, Prabhakar R, Seth A. A prospective study evaluating surgery and chemoradiation in muscle invasive bladder cancer. J Cancer Res Ther 2007;3:81-5.
5. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization / International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. Am J Surg Pathol 1998;22:1435-48.
6. Ismaili N, Elkarak F, Heudel PE, Flechon A, Droz JP. Small cell cancer of the bladder: The Leon-Berard cancer centre experience. Indian J Urol 2008;24: 494-7.
7. Abrahams NA, Moran C, Reyes AO, Siefker-Radtke A, Ayala AG. Small cell carcinoma of the bladder: A contemporary clinicopathological study of 51 cases. Histopathology 2005;46:57-63.

8. Grignon DJ, Ro JY, Ayala AG, Shum DT, Ordóñez NG, Logothetis CJ, *et al.* Small cell carcinoma of the urinary bladder: A clinicopathologic analysis of 22 cases. Cancer 1992;69:527-36.
9. Iczkowski KA, Shanks JH, Allsbrook WC, Lopez-Beltran A, Pantazis CG, Collins TR, *et al* . Small cell carcinoma of urinary bladder is differentiated from urothelial carcinoma by chromogranin expression, absence of CD44 variant 6 expression, a unique pattern of cytokeratin expression, and more intense gamma-enolase expression. Histopathology 1999;35:150-6.
10. Siefker-Radtke AO, Dinney CP, Abrahams NA, Moran C, Shen Y, Pisters LL, *et al.* Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: A retrospective review of the M. D. Anderson cancer experience. J Urol 2004;172:481-4.
11. Cheng L, Pan CX, Yang WJ, Lopez-Beltran A, MacLennan GT, Haiqun L, *et al* . Small cell carcinoma of the urinary bladder: Aclinicopathologic analysis of 64 patients. Cancer 2004;101:957-62.
12. Choong NW, Fernando Quevedo J, Kaur JS. Small cell carcinoma of the urinary bladder: The Mayo Clinic experience. Cancer 2005;103:1172-8.
13. Sved P, Gomez P, Manoharan M, Civantos F, Soloway MS . Small cell carcinoma of the bladder. BJU Int 2004;94:12-7.
14. Puente S, Velasco A, Gallel P, Pallares J, Perez-Ruiz L, Ros S, *et al* . Metastatic small cell carcinoma to the thyroid gland: A pathologic and molecular study demonstrating the origin in the urinary bladder. Endocr Pathol 2008;19:190-6.
15. Bex A. Review: Treatment of small cell carcinoma of the urinary bladder: Can we learn from small cell lung cancer? Clin Adv Hematol Oncol 2008;6:385-6.
16. Pan CX, Zhang H, Lara PN Jr, Cheng L. Small-cell carcinoma of the urinary bladder: Diagnosis and management. Expert Rev Anticancer Ther 2006;6: 1707-13.
17. Rogers CG, Palapattu GS, Shariat SF, Karakiewicz PI, Bastian PJ, Lotan Y, *et al* . Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder. J Urol 2006;175:2048-53.
18. Bastus R, Caballero JM, Gonzalez G, Borrat P, Casalots J, Gomez de Sequra G. Small cell carcinoma of the urinary bladder treated with chemotherapy and radiotherapy: Results in five cases. Eur Urol 1999;35:323-6.
19. Lohrisch C, Murray N, Pickles T. Small cell carcinoma of the bladder: Long term outcome with integrated chemoradiation. Cancer 1999;86: 2346-52.
20. Bex A, de Vries R, Pos F, Kerst M, Horenblas S. Long-term survival after sequential chemoradiation for limited disease small cell carcinoma of the bladder. World J Urol 2009;27:101-6.
21. Black PC, Brown GA, Dinney CP. The impact of variant histology on the outcome of bladder cancer treated with curative intent. Urol Oncol 2009;27: 3-7.
22. Ismaili N, Arifi S, Flechon A, El Mesbahi O, Blay JY, Droz JP, *et al* . Small cell cancer of the bladder: Pathology, diagnosis, treatment and prognosis. Bull Cancer 2009;96:E1-E15.
23. Quek ML, Nichols PW, Yamzon J, Daneshmand S, Miranda G, Cai J, *et al* . Radical cystectomy for primary neuroendocrine tumors of the bladder: The university of southern California experience. J Urol 2005;174:93-6.