Rare Presentation of Small Cell Neuroendocrine Carcinoma of Urinary Bladder

Authors
Dr Mamta Chaudhary¹, Dr Prachi Gupta¹, Dr Ml Yadav², Dr Shweta Sharma³
¹Resident Pathology, ²Prof. Pathology, ³Assist Prof. Pathology

Abstract
Small cell type neuroendocrine carcinoma of the bladder is a rare and aggressive tumour associated with poor prognosis. It often presents at a late stage than urothelial carcinoma of the bladder and comprises less than 1% of the bladder malignancies.

We report a case of 72 year old male diagnosed with a 5 x 2.8 cm mass in urinary bladder at anterior and left lateral wall of urinary bladder. He underwent surgery – a radical cystoprostactectomy with standard lymph node dissection. The histomorphological report showed poorly differentiated carcinoma in favor of small cell neuroendocrine carcinoma showing perineural invasion and metastatic carcinoma in lymph node.

Introduction
Neuroendocrine carcinoma of urinary bladder is an extremely rare pathology, accounting for only 0.35%-0.70% of all bladder cancers.¹ The first report on small cell invasive bladder cancer was published in 1981 by carmer et al.²

Bladder small cell carcinoma most commonly presents in the seventh decade with a mean age of presentation at approximately 67 years.¹ In both small cell carcinoma and urothelial carcinoma of urinary bladder, the most common presentation is painless gross hematuria (67%-100% in bladder small cell carcinoma) with or without dysuria.³

Prognosis is dependent on performance status and the extent of disease at diagnosis, whereas overexpression of p53, patient age, sex, and presenting symptom do not appear to correlate with prognosis.⁴

The diagnosis of bladder small cell carcinoma can be made solely on morphologic grounds, with the help of immunohistochemistry to document neuroendocrine differentiation. Conventional neuroendocrine marker have low sensitivity for bladder small cell carcinoma.

Case Report
We report the case of a 72 year old male who was admitted to the urology department with the complaint of hematuria and pain abdomen. Past history was not significant.

Abdominal ultrasound at Curewell diagnostic centre corroborated these findings, showing an ill defined, irregular hypoechoic mass of approximately 5cm x 2.8cm with internal vascularity is seen arising from right posterolateral wall of urinary bladder and projecting into the urinary bladder lumen like urinary bladder mass. Prostate is enlarged in size and measures about 41.5mm x 41.1mm x 31.8mm,
volume 28.4cc. There is protrusion of medial lobe about 7.5mm in bladder base. CECT of whole abdomen with urography, shows large irregular enhancing mass is seen involving right lateral and posterior wall of urinary bladder, invading right vesico-ureteric junction causing mild right hydroureteronephrosis, with perivesical fat standing, lost fat planes between the lesion and prostate with altered attenuation of prostate suggests its invasion. Enhancing nodular lesion at anterior and left lateral wall of urinary bladder – likely malignant urinary bladder mass. Cystoscopy showed a proximal urethral narrowing seen which is dilated. Prostate was normal. In the bladder growth seen involving right lateral,right infero-lateral surface, right side half of trigone and bladder neck. Right ureteric orifice was not visualized and left ureteric orifice was normal. Radical cystoprostactomy with standard lymph node resection was done.

On histological examination –poorly differentiated carcinoma-histogenesis uncertain. Morphology is in favour of small cell neuroendocrine carcinoma. The tumor shows infiltration through the whole thickness of bladder wall and is infiltrating into surrounding fibro-adipose tissue. Lymphovascular invasion is not seen. Tumor shows occasional focus of perineural invasion. Prostate – benign prostatic hyperplasia, infiltration by tumor tissue I not seen. 2 out of total 27 resected lymph nodes showing metastatic carcinoma.

AJCC 2017 TNM STAGING T3a N2 Mx

Discussion
More than 90% of bladder cancers are urothelial carcinomas. The two most common non urothelial
epithelial malignancies of bladder are squamous cell carcinoma and adenocarcinoma. Neuroendocrine carcinoma are less common than the above histologic varients in the genitourinary systems and are classified into two subtypes-carcinoid tumor and neuroendocrine carcinoma, neuroendocrine carcinoma is further devided into small cell carcinoma (SmCC) and large cell carcinoma, the latter of which is exceeding rare in the bladder. The origin of small cell carcinoma bladder is uncertain but different hypothesis have been postulated. The most important hypothesis were- 1) Malignant transformation of bladder neuroendocrine cells gives rise to bladder small cell carcinoma. 2) small cell carcinoma bladder arises from urothelial metaplastic changes. 3) last and most powerfull hypothesis suggests that the origin of small cell carcinoma bladder may be a multipotential common stem cell that has ability to differentiate into various cell types depending upon the influence. This theory may explains the co existence of small cell carcinoma bladder with transitional cell carcinoma and the heterogenecity of immunohistochemical staining. The age, gender predilection and symptoms at presentation of bladder small cell carcinoma are similar to those of urothelial carcinoma of bladder. Gross hematuria is the most common symptom in small cell carcinoma bladder which was noted in 63%-88% of cases. Dysuria has been reported the second most common symptom. Other symptoms like irritable symptoms, pelvic pain, recurrent urinary infection, urinary obstruction and general symptoms like weight loss and fatigue may occur. Exceptionally paraneoplastic syndromes like cushing syndrome, hypercalcemia, hypophosphatemia also mentioned sometimes. Cigarette smoking is a risk factor for small cell carcinoma bladder with 50%-70% of patients reporting a smoking history. Bladder small cell carcinoma more often presents at a later stage than the urothelial carcinoma. Many patients with bladder small cell carcinoma have some common , non specific risk factors , including bladder calculi , bladder manipulation and chronic cystitis. Bladder small cell carcinoma presents as stage I in 0%-5% of patients, stage II in 27%-44% of patients, stage III in 24%-30% of patients and stage IV in 27%-43% of patients. Diagnosis of small cell carcinoma bladder is mainly by histopathological examination of specimens. Immunohistochemical staining is extremely helpful in establishing the diagnosis. Histologically bladder small cell carcinoma is identical to small cell carcinoma of the other sites. Tumor usually has a pattern less type of diffuse growth, occasionally nest and trabeculae are observed. Cells having scant cytoplasm containing few organelles. Pyknotic round to oval nuclei and evenly dispersed salt and pepper chromatin. Frequent mitosis, crush artifacts, geographic necrosis, azzopardi effects are indicative of its high proliferation rate. In most reports showed a high incidence of mixed small cell carcinoma than the pure small cell carcinoma. It has been found that pure small cell carcinoma tends to have a poorer outcome than mixed small cell carcinoma bladder. Immunohistochemical markers commonly used to demonstrate neuroendocrine differentiation. These markers are neuron specific enolase (NSE), chromogranin A (CGA), synaptophysin, cytokeratin, TTF1. Most commonly positive markers are neuron specific enolase (25%-100%), chromogranin A (22%-89%), synaptophysin (67%-76%). Chromogranin A ; in case of bladder small cell carcinoma, chromogranin A is the least sensitive of neuroendocrine markers , staining one third to one half of bladder small cell carcinoma cases. It is positive only in 5% of bladder urothelial carcinoma cases. Synaptophysin; in bladder small cell carcinoma the sensitivity of synaptophysin and CD56 is
moderately higher than that of chromogranin A. A recent study has reported that CD56 may be the most sensitive neuroendocrine marker.

3) Neuron specific enolase; NSE is expressed in about 80% of bladder small cell carcinoma or more, but the specificity is very low.21

4) Epithelial markers that can be present in small cell carcinoma are cytokeratin 7, CAM 5.2 and CK 8/18. Cytokeratin CAM 5.2 is present in both urothelial carcinoma and small cell carcinoma, but the pattern of staining are different

In urothelial carcinoma – along the membrane
In small cell carcinoma – perinuclear pattern.22

Small cell carcinoma of the urinary bladder may be mistaken for poorly differentiated urothelial carcinoma, malignant lymphoma, metastasis from other neuroendocrine tumor (lung), neuroendocrine carcinoma of prostate infiltrating the bladder.

Because of the rarity of small cell carcinoma bladder, there is no standard treatment of the disease.

Treatment options are:

i. Chemotherapy alone.
ii. Neoadjuvant chemotherapy followed by cystectomy.
iii. Cystectomy followed by adjuvant chemotherapy
iv. Cystectomy alone.
v. Transurethral resection of bladder alone.
vi. Radiotherapy alone.
vii. Concurrent or sequential chemotherapy and radiotherapy.

The prognosis of small cell carcinoma bladder is poor. Five year survival rate of all stages combined to 19%. Pure small cell carcinoma histology was shown to have poorer outcome than mixed small cell carcinoma.1,11

Conclusion

Small cell carcinoma of the urinary bladder is a rare, often fatal disease. Its presenting age, sex predilection, symptoms, and gross morphology are similar to those of conventional urothelial carcinoma, whereas its biologic behavior is much more aggressive when compared with stage matched urothelial carcinoma. Metastasis is common and prognosis is poor.

Bladder small cell carcinoma usually present at a later stage than urothelial carcinoma and therefore confers a worse prognosis.

Even at an early stage radical treatment is required because small cell carcinoma of the bladder has a propensity for early metastasis.

Diagnosis of small cell carcinoma bladder depends on pathology and immunohistochemistry. Radical bladder cystectomy with combined chemotherapy and radiotherapy can improve survival time.

References

1. Choong NW, Quevedo JF, Kaur JS. Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer. 2005;103(6):1172–1178. [PubMed]

2. Cramer SF, Aikawa M, Cebelin M. Neurosecretory granules in small cell invasive carcinoma of the urinary bladder. Cancer. 1981;47:724–30

3. Church DN, Bahl A. Clinical review—small cell carcinoma of the bladder. Cancer Treat Rev. 2006;32(8):588–593.

4. Naturale RT, Maclennan GT. Small cell carcinoma of the bladder. J Urol. 2006;176(2):781.

5. Mazzucchelli R, Morichetti D, Lopez-Beltran A, et al. Neuroendocrine tumours of the urinary system and male genital organs: clinical significance. BJU Int. 2009;103(11):1464–1470

6. Ali SZ, Reuter VE, Zakowski MF. Small cell neuroendocrine carcinoma of the urinary bladder: a clinicopathologic study with emphasis on cytologic features. Cancer. 1997;79:356–361. doi: 10.1002/(SICI)1097-0142(19970115)79:2<356::AID-CNCR19>3.0.CO;2-. [PubMed] [Cross Ref]

7. Oesterling JE, Brendler CB, Burgers JK, Marshall FF, Epstein JI. Advanced small
cell carcinoma of the bladder. Successful treatment with combined radical cystoprostatectomy and adjuvant methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy. Cancer. 1990;65(9):1928–36. doi: 10.1002/1097-0142(19900501)65:9<1928::AID-CNCR2820650910>3.0.CO;2-X. [PubMed] [Cross Ref]

8. Terracciano L, Richter J, Tornillo L, Beffa L, Diener PA, Maurer R, Gasser TC, Moch H, Mihatsch MJ, Sauter G. Chromosomal imbalances in small cell carcinomas of the urinary bladder. J Pathol. 1999;189(2):230–5. doi: 10.1002/(SICI)1096-9896(199910)189:2<230::AID-PATH407>3.0.CO;2-8. [PubMed] [Cross Ref]

9. Christopher ME, Seftel AD, Sorenson K, Resnick MI. Small cell carcinoma of the genitourinary tract: an immunohistochemical, electron microscopic and clinicopathological study. J Urol. 1991;146(2):382–8. [PubMed]

10. van Hoeven KH, Artymyshyn RL. Cytology of small cell carcinoma of the urinary bladder. Diagn Cytopathol. 1996;14 (4):292–7. doi: 10.1002/(SICI)1097-0339(199605)14:4<292::AID-DC3>3.0.CO;2-I. [PubMed] [Cross Ref]

11. Cheng L, Pan CX, Yang XL, Lopez-Beltran A, MacLennan GT, Lin H, Kuzel TM, Papavero V, Tretiakova M, Nigro K, Koch MO, Eble JN. Small cell carcinoma of the urinary bladder: A clinicopathologic analysis of 64 patients. Cancer. 2004;101 (5):957–962. doi: 10.1002/cncr.20456. [PubMed] [Cross Ref]

12. 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(1):57–63. doi: 10.1111/j.1365-2559.2004.01980.x. [PubMed] [Cross Ref]

13. Siefker-Radtke AO, Dinney CP, Abrahams NA, Moran C, Shen Y, Pisters LL, Grossman HB, Swanson DA, Millikan RE. 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(2):481–4. doi: 10.1097/01.ju.0000132413.85866.fc. [PubMed] [Cross Ref]

14. Blomjous CEM, Vos W, De Voogt HJ, van der Valk P, Meijer CJLM. Small cell carcinoma of the urinary bladder. A clinicopathologic, morphologic, immunohistochemical and ultrastructural study of 18 cases. Cancer. 1989;64(6):1347–57. doi: 10.1002/1097-0142(19890915)64:6<1347::AID-CNCR2820640629>3.0.CO;2-Q. [PubMed] [Cross Ref]

15. Liang Cheng, Chong-Xian Pan, Ximing JYang, et al. Small cell carcinoma of the bladder a clinicopathologic analysis of 64 patients. American Cancer Society.2004;101(5):957-962.

16. Chekrine T, De Bari B, Cassier P, et al. Carcinome neuroendocrine à petites cellules de la vessie: À propos d’une observation et revue de la littérature. Cancer/Radiothérapie. 2011;15:250-253.

17. Sved P, Gomez P, Manoharan M, Civantos F, Soloway MS. Small cell carcinoma of the bladder. BJU Int. 2004;94(1):12–17. doi: 10.1111/j.1464-410X.2003.04893.x. [PubMed] [Cross Ref]

18. Ismaili N, Heudel PE, Elkarak F, et al. Outcome of recurrent and metastatic small cell carcinoma of the bladder. BMC Urol. 2009;9:4. [PMC free article] [PubMed]

19. Moretto P, Wood L, Emmenegger U, Blais N, Mukherjee SD, Winquist E, et al. Management of small cell carcinoma of the bladder: Consensus guidelines from the Canadian Association of Genitourinary Medical Oncologists (CAGMO) Can Urol
Assoc J. 2013;7(1–2):E44–56. [PMC free article] [PubMed]
20. Mukesh M, Cook N, Hollingdale AE, Ainsworth NL, Russell SG. Small cell carcinoma of the urinary bladder: a 15-year retrospective review of treatment and survival in the Anglian Cancer Network. BJU Int. 2009;103(6):747–752.
21. Soriano P, Navarro S, Gil M, Llombart-Bosch A. Small-cell carcinoma of the urinary bladder: a clinico-pathological study of ten cases. Virchows Arch. 2004;445(3):292–297.
22. Manunta A, Vincendeau S, Kiriakou G, Lobel B, Guillé F. Non-transitional cell bladder carcinomas. BJU Int. 2005;95:497–502. [PubMed]