



Rare Presentation of Small Cell Neuroendocrine Carcinoma of Urinary Bladder

Authors

Dr Mamta Chaudhary¹, Dr Prachi Gupta¹, Dr MI 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 cystoprostatectomy 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.¹The 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.¹In 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 x2.8cm 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.

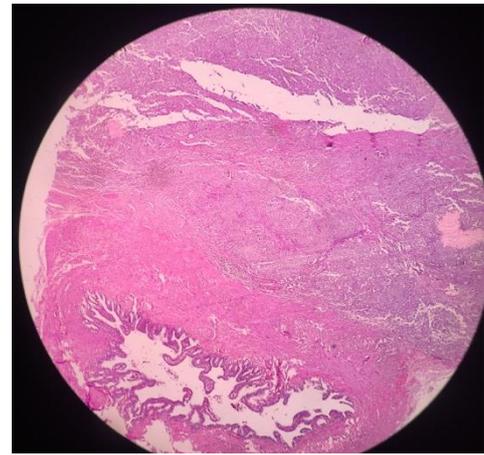
CECT of whole abdomen with urography, shows large irregular enhancing mass is seen involving right lateral and posterior wall of urinary bladder, invading right vesico-ureteric junction causing mild right hydronephrosis, with perivesical fat standing, lost fat planes between the lesion and prostate with 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 cystoprostatectomy 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.

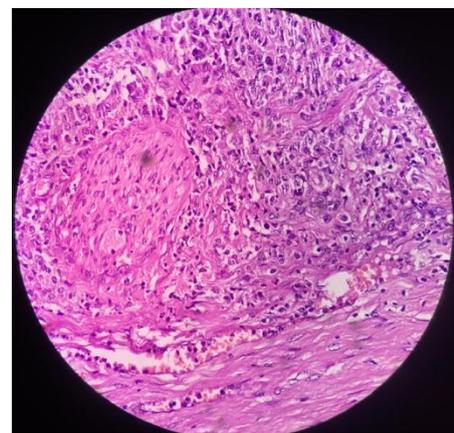
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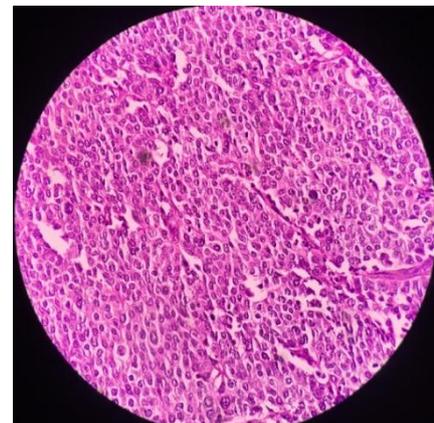
a. Showing gross picture of bladder showing mass



b. 4x picture of bladder showing dark tumor cells



c. 10x picture showing perineural invasion by tumor cells



d. 40x picture showing tumor cell, nuclei of cells are irregular, with scanty cytoplasm, some showing spots of nuclear clearing s/o salt and pepper.

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 variants in the genitourinary systems and are classified into two subtypes- carcinoid tumor and neuroendocrine carcinoma, neuroendocrine carcinoma is further divided into small cell carcinoma (SmCC) and large cell carcinoma, the latter of which is exceeding rare in the bladder.⁵

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.⁶

2) small cell carcinoma bladder arises from urothelial metaplastic changes.^{1,7}

3) last and most powerful 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 explain the co existence of small cell carcinoma bladder with transitional cell carcinoma and the heterogeneity of immunohistochemical staining.^{8,9,10}

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.^{1,11,12,13} Dysuria has been reported the second most common symptom.^{13,14} Other symptoms like irritable symptoms, pelvic pain, recurrent urinary infection, urinary obstruction and general symptoms like weight loss and fatigue may occur.^{15,1,16}

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.³ Many patients with bladder small cell carcinoma have some common, non specific risk factors, including bladder calculi, bladder manipulation and chronic cystitis.³

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.³

Diagnosis of small cell carcinoma bladder is mainly by histopathological examination of specimens. Immunohistochemical staining is extremely helpful in establishing the diagnosis.

¹⁷Histologically 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.¹² 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.¹⁸

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%).¹⁹

1) 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.¹² It is positive only in 5% of bladder urothelial carcinoma cases.²⁰

2) 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.

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