

Pure primary small cell carcinoma of urinary bladder: A rare diagnostic entity

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Abstract

Small cell carcinoma of the bladder is a rare, aggressive, poorly differentiated neuroendocrine neoplasm accounting for only 0.3-0.7% of all bladder tumors. Since the tumor is very rare, pathogenesis is uncertain. Small cell carcinomas of the urinary bladder are mixed with classic urothelial carcinomas or adenocarcinomas of the bladder in 68% cases, making pure primary small cell carcinoma even a rarer entity. The unknown etiology and natural history of small cell carcinoma of the urinary bladder represent a challenge both to the pathologist and urologists for its diagnosis and treatment, respectively.

Key Words: Pure, primary, small cell carcinoma, urinary bladder

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INTRODUCTION

Small cell carcinoma of the bladder is a rare, aggressive, poorly differentiated neuroendocrine neoplasm accounting for only 0.3-0.7% of all bladder tumors.^[1,2]

Since the tumor is very rare, pathogenesis is uncertain. Hypotheses sustain urothelial cell origin, malignant transformation of neuroendocrine cells of urinary bladder and stem cell theory. Recently, molecular studies have indicated that small cell carcinoma and urothelial cancer are derived from the same clonal population, though the tumor is still classified as a discrete entity.^[1,3]

We hereby report a case of small cell carcinoma of urinary bladder, initially reported as poorly differentiated urothelial carcinoma on transurethral resection of bladder tumor

specimen to emphasize its rarity as well as the role of immunohistochemistry to differentiate between the two.

CASE REPORT

A 59-year-old male presented in the outpatient department of Urology, R G Kar Medical College and Hospital, Kolkata with the chief complaint of mild hematuria, particularly at the end of the micturition. Patient was a builder by profession and a chronic smoker. His past and family history was insignificant.

The patient's urine examination was positive for occult blood with microscopic presence of 3-6 RBC/hpf and negative growth on culture. Ultrasonograph of the urinary bladder revealed a large papillomatous mass measuring 5 × 4 cm arising from left supralateral wall of urinary bladder with no evidence of calculi. Contrast-enhanced computed tomography scan confirmed the anatomical location of the mass along with involvement of the adjacent musculature [Figure 1a]. Patient underwent cystoscopy with biopsy of mass, which on histopathological examination was reported as poorly differentiated urothelial carcinoma.

Radical cystoprostatectomy with pelvic lymphadenectomy along with Studer's neobladder reconstruction was done with

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ileal wall and the specimen was sent to the Department of Pathology for histopathological examination. Postoperative period was uneventful. Combined ascending and micturating cystourethrography done 4 weeks postsurgery, showed normal flow of contrast through penile urethra in ascending urethrogram along with normal outline of neobladder exhibiting feathery pattern of small intestine [Figure 2].

PATHOLOGICAL EXAMINATION

On gross, the composite specimen of urinary bladder, prostate with seminal vesicles, part of both sided ureters and perivesical adipose tissue measured $14 \times 9 \times 6.5$ cm. On cutting, the urinary bladder showed a polypoidal mass measuring 5.5 cm in its greatest dimensions [Figure 1b]. Sections from the representative areas on microscopy showed sheets and nests of loosely cohesive, small round to oval cells with hyperchromatic coarsely granular nuclear chromatin and scant cytoplasm. Mitotic figures were frequent and at focal areas, nuclear molding and muscle invasion was seen [Figures 3a and b]. The neoplastic cells on immunohistochemistry exhibited Chromogranin A and focal cytokeratin positivity and were negative for epithelial membrane antigen, leucocyte common antigen, synaptophysin and CD56.

After the histopathological diagnosis of small cell carcinoma urinary bladder, patient was advised three cycles of chemotherapy and till date, he is keeping well.

DISCUSSION

Neuroendocrine tumors can arise in almost all epithelium-containing organs and are commonly encountered in the respiratory and gastrointestinal tract while involvement of the urinary bladder is very rare. Small cell carcinoma of the bladder is similar to small cell carcinoma of the lung in clinical behavior, with wide age range (20-91 years) and 3-5:1 male female ratio. Cigarette smoking, bladder calculi and long-term cystitis are thought to be the etiological factors involved in its pathogenesis.^[3-5]

Patients typically present with hematuria in 88% and history of smoking cigarettes in 65% cases. Tumors are usually large and polypoid or nodular and may have an ulcerated surface. Other symptoms such as local irritation, pelvic pain and urinary obstruction are also reported in the literature. Rarely, patients can develop distant metastases or paraneoplastic syndromes.^[6] The present patient was also a known chronic smoker and presented with hematuria only. No evidence of distant metastasis, paraneoplastic syndrome or primary neuroendocrine tumor of other organ was detected.

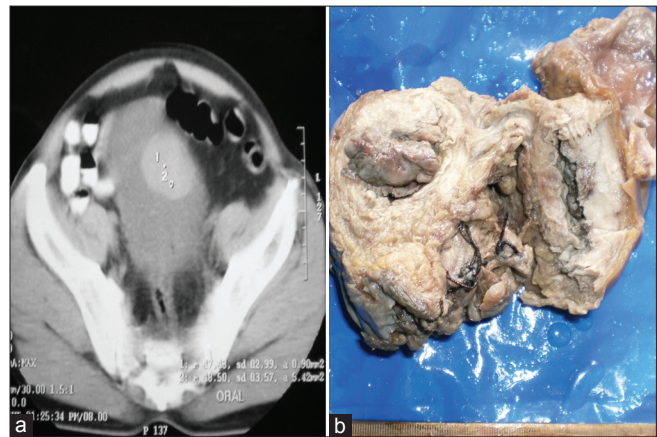


Figure 1: (a) Contrast-enhanced CT scan showing papillomatous mass arising from left supralateral wall of UB. (b) Radical cystectomy specimen, confirmed the CT scan report



Figure 2: Combined ascending and micturating cystourethrogram showing normal flow of contrast through penile urethra in ascending urethrogram along with normal outline of neobladder exhibiting feathery pattern of small intestine

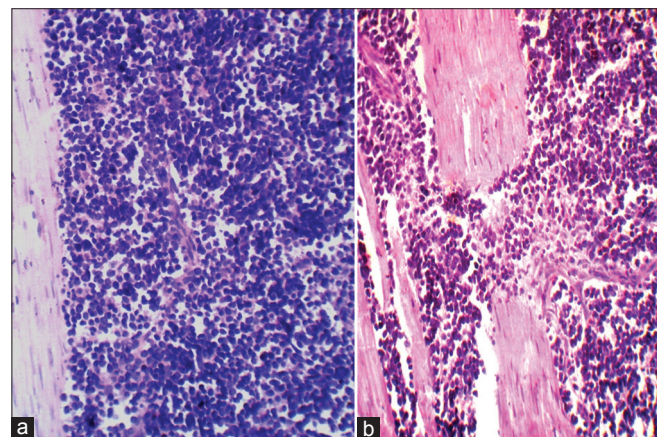


Figure 3: (a) Sheets and nests of loosely cohesive, small round to oval cells with hyperchromatic coarsely granular nuclear chromatin and scant cytoplasm. (b) Note the muscle invasion and mitotic figures (H and E, $\times 400$)

The lateral bladder walls are the most common site. Wall invasion is typical, with masses ranging from 3 to 8 cm and central necrosis or cystic change may be seen with CT scan.^[4,5] The present case even though presented with a large polypoidal mass involving the lateral wall and muscle layers, central necrosis or cystic change was not detected on CT scan.

Small cell carcinoma of the urinary bladder are mixed with classic urothelial carcinomas or adenocarcinomas of the bladder in 68% cases^[4] but the present case even after repeat sectioning of tumor from different areas did not reveal evidence of urothelial carcinoma. Sometimes, features of metastatic small cell carcinoma of lung origin are indistinguishable from small cell carcinoma urinary bladder on the basis of histology alone.^[7] Immunohistochemistry helps to differentiate between them and other vast differential diagnosis such as high-grade urothelial carcinoma, lymphoma, carcinoid, lymphoepithelial-like carcinoma from lung.^[4,7]

Neuroendocrine markers, such as chromogranin A, synaptophysin, CD56, and neuronal-specific enolase, are often focal or diffusely positive for these tumors by immunohistochemical method. A cocktail of cytokeratin markers is often nonreactive, but low molecular cytokeratin, CAM5-2, and epithelial membrane antigen are mostly positive.^[8] However, sometimes the immunohistochemical method fails to demonstrate expression of these markers and a definitive diagnosis can be rendered based on morphology alone.^[7] The typical microscopic features are hypercellularity, necrosis, nuclear chromatin crush artefact and mitoses.^[6] The present case had typical microscopic features appreciated on cystectomy specimen but varied immunohistochemical markers expression. The neoplastic cells showed diffuse positivity for chromogranin A but were negative for synaptophysin and epithelial membrane antigen. Thus, a definitive diagnosis was rendered considering both the microscopic as well as immunohistochemical features.

Unfortunately, the optimal management is not well defined. Therapeutic modalities vary and include transurethral resection, cystectomy, radiation therapy and systemic chemotherapy.^[9] Surgical resection (radical cystectomy and extended pelvic lymphadenectomy) alone is unlikely to be curative, unless the tumor is confined to the bladder. Combination therapy with adjuvant or neoadjuvant chemotherapy appears beneficial.^[10]

Despite therapy, the long-term prognosis is poor, with a 16% 5-year survival. Lymph node metastases occur in 66% of cases, with distant metastases occurring in the liver, bone and lung.^[4] The present case though presented with a large tumor mass along with muscle invasion, responded well to combination therapy of surgical resection followed by systemic chemotherapy.

Thus, to conclude, the unknown etiology and natural history of small cell carcinoma of the urinary bladder represent a challenge both to the pathologist and urologists for its diagnosis and treatment respectively. As a result of the rarity of this neoplasm, consensus of opinion for its optimum management is difficult to achieve. Therefore different treatment strategies and a large group study to know the clinical behavior of this uncommon tumor should be reported in order to improve its poor prognosis.

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