

A varied morphological spectrum of urinary bladder carcinoma - A rare diagnostic entity

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Received: 23rd October, 2018

Accepted: 25th December, 2018

Abstract

Bladder carcinoma is the seventh most common malignancy worldwide and multiple risk factors have been linked to bladder cancer. Urothelial carcinoma accounts for the most common histological subtype and has a propensity for divergent differentiation. The clinical outcome of some of the variants differs from the typical urothelial carcinoma and recognition of these variants is pertinent. Primary small cell carcinoma is an extremely rare malignant neoplasm which accounts for less than 1% of urinary bladder cancer. We present two cases of bladder carcinoma in elderly men with varied histomorphological subtypes which posed a diagnostic challenge.

Keywords: Bladder carcinoma, Primary small cell carcinoma, Hypercalcemia, High grade urothelial carcinoma, Glandular differentiation.

Introduction

Urothelial carcinoma is the major cause of morbidity and mortality throughout the world. It is three times more common in men than in women and is seen in patients over 50yrs of age. An association with cigarette smoking is well substantiated.¹ The diverse morphology and differentiation of urothelial carcinoma has resulted in increasing number of histologic variants being recognized. 40% of invasive high grade urothelial carcinoma contains foci of squamous differentiation in contrast to glandular differentiation seen in upto 18% of cases.² Small cell carcinomas (neuroendocrine carcinomas) that are histologically similar to pulmonary tumor occur in the bladder, which account for approximately 0.5% of the malignant bladder tumors.³ They are typically seen in elderly and association with hypercalcemia is rare.⁴ In contrast to the pulmonary counterpart small cell carcinoma of bladder is rarely associated with neoplastic syndromes.⁵ Pure small cell carcinoma of the bladder is infrequent and is usually mixed with another histological subtype, most commonly urothelial carcinoma.⁶

Case Reports

Case 1

A 65 year old gentleman, a known case of Type II Diabetes Mellitus and dyslipidemia presented with complaints of low back pain and dysuria, associated with history of recurrent fever and urinary tract infection. Biochemical investigations revealed hypercalcemia with elevated liver enzymes. Serum bilirubin was within normal limits. Haematological parameters revealed normocytic normochromic anaemia. Ultrasound KUB revealed a broad based polypoidal hypoechoic lesion along the right anterior wall of urinary bladder with fine echogenic foci suggestive of calcification [Fig. 1a]. Computerized tomography of the chest and abdomen showed multiple well defined target lesions of both lobes of the liver suggesting metastasis [Fig.

1b]. Transurethral resection of bladder tumor was done to evaluate the morphology of tumor. Microscopy showed diffuse ulceration of the urothelial lining, with only a focally preserved urothelium. The lamina propria and submucosa showed infiltration by a high grade malignant neoplasm with single cell infiltration into the urothelium above [Fig. 2]. The tumor was arranged in diffuse sheets and ill-defined nests. The cells showed round to oval markedly pleomorphic nuclei with moulding, coarse chromatin, inconspicuous nucleoli and scanty cytoplasm. Foci of apoptotic bodies and brisk atypical mitosis were noted [Fig. 3]. The tumor was interspersed by confluent and punctuate geographic necrosis. The tumor infiltrated the muscularis propria and showed a focus of lymphovascular tumor emboli [Fig. 3 inset]. No other urothelial component, neither squamous nor glandular differentiation was evident. Immunohistochemistry done showed diffuse positivity for Synaptophysin, CD 56, p53 and with Ki 67 proliferative index of 90% [Fig. 4]. CK7, CK20 positivity was confined only to the preserved lining urothelium. PSA, TTF-1 and EMA were negative. In view of the histomorphological features with diffuse positivity for neuroendocrine markers and negativity for Cytokeratin a diagnosis of Primary Small Cell Carcinoma of the Urinary bladder was rendered with a probable metastasis to the liver. Patient was unwilling for a liver biopsy and refused further treatment.

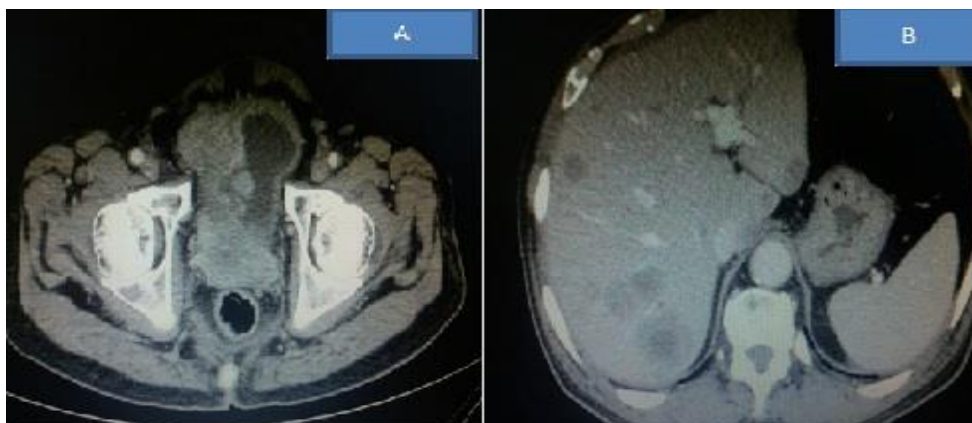


Fig. 1a: Ultrasound KUB showing a broad based polypoidal hypoechoic lesion along the Right anterior wall of urinary bladder with fine echogenic foci suggestive of calcification. **Fig 1b:** CT of the chest and abdomen showing multiple well defined target lesion of both lobes of liver suggestive of metastasis

Case 2

A 74 year old male patient presented with history of dysuria and haematuria of 3 months duration, followed by acute retention of urine, 2 days prior to admission. Cystoscopic examination done revealed a large polypoidal bladder mass involving the anterolateral wall of the urinary bladder. A transurethral resection of bladder mass was done. Histopathology revealed focally preserved urothelium with a necrotic malignant tumor showing three distinct morphological components. At one area was seen a high grade urothelial carcinoma with tumor arranged in solid and fused papillary pattern composed of cells with round to oval pleomorphic nuclei with coarse chromatin few showing prominent nucleoli and moderate eosinophilic cytoplasm with foci of mitosis [Fig. 5]. Focal glandular differentiation was seen showing atypical glands with round to oval stratified nuclei with scanty cytoplasm and with mitosis [Fig. 5 Inset A]. Also evident were detached fragments of a high grade neoplasm with neuroendocrine morphology arranged predominantly in solid sheets showing round to oval markedly pleomorphic nuclei with hyperchromasia showing nuclear moulding with inconspicuous nucleoli and scanty cytoplasm [Fig. 5 Inset B]. Foci of atypical mitosis and apoptotic bodies were evident. Immunohistochemistry done showed urothelial and glandular components showing positivity for CK7, CK20 and EMA with the neuroendocrine component showing diffuse positivity for Synaptophysin [Fig. 6]. TTF 1 and p53 was negative. Ki-67 proliferation index was 70%. In view of the histomorphological and immunohistochemical features a diagnosis of High grade urothelial carcinoma with glandular differentiation and with coincident small cell carcinoma was rendered. Patient was referred to the medical oncologist but lost to follow up.

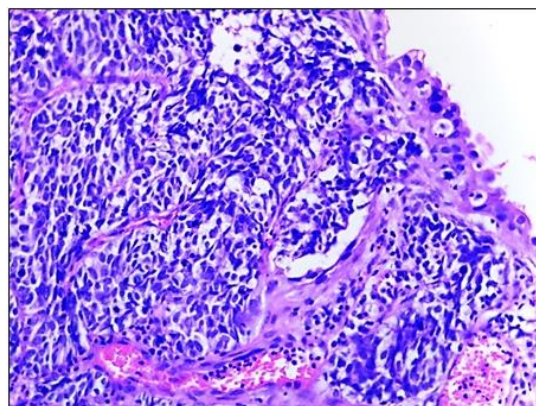


Fig. 2 : Photomicrograph showing ulceration of the urothelial lining with only focally preserved urothelium. The lamina propria and submucosa showing infiltration by a high grade malignant neoplasm with single cell infiltration into the overlying urothelium (H&E 10x)

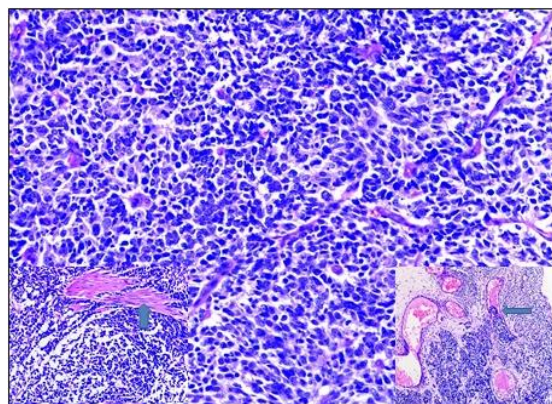


Fig. 3: Microphotograph showing cells with round to oval markedly pleomorphic nuclei with moulding, coarse chromatin, inconspicuous nucleoli and scanty cytoplasm with apoptosis and mitosis seen infiltrating the muscularis as depicted by an arrow. Inset showing lymphovascular emboli (H&E 20x)

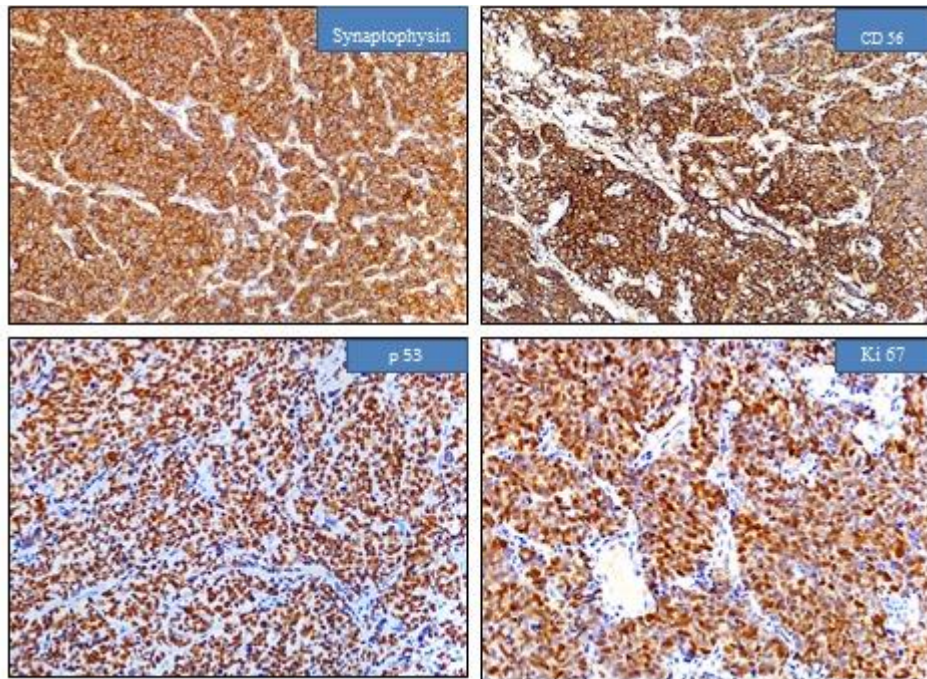


Fig. 4: IHC showing diffuse positivity for Synaptophysin, CD56 and p53 with Ki-67 proliferative index of 90%

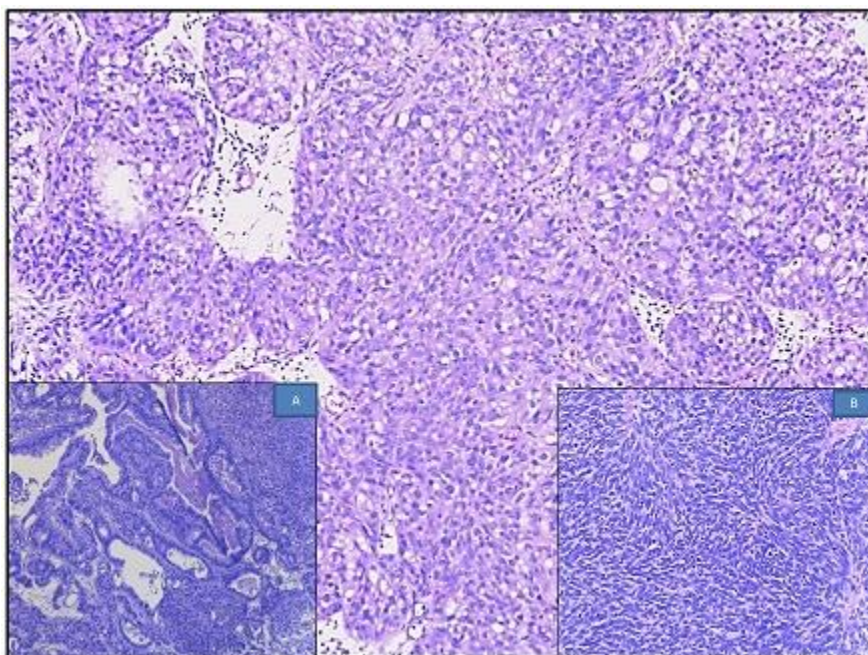


Fig. 5: Photomicrograph showing high grade urothelial carcinoma with tumor arranged in solid and fused papillary pattern with cells showing round to oval pleomorphic nuclei, with coarse chromatin, prominent nucleoli, moderate eosinophilic cytoplasm and foci of mitosis. Inset (A) showing glandular differentiation and Inset (B) showing a neuroendocrine tumor (H&E 20x)

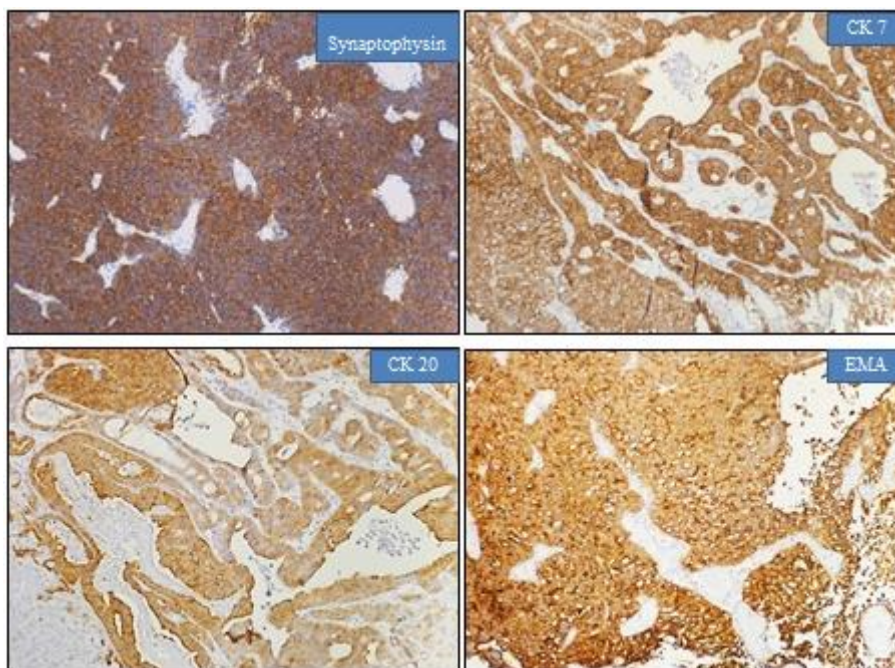


Fig. 6: IHC showing urothelial and glandular component with positivity for CK7, CK20 and EMA, with neuroendocrine component showing positivity for Synaptophysin

Discussion

Primary small cell carcinoma of the urinary bladder is extremely rare and constitutes less than 1% of urinary bladder tumors. It is very aggressive and refractory to treatment due to its higher metastatic capability, compared to other bladder tumors.⁷ More than 60% of the reported cases were metastatic at diagnosis⁸ with metastasis to regional lymph nodes, bone, liver or lung.

Small cell carcinoma of urinary bladder originates from multipotential undifferentiated stem cells as supported by the fact that small cell carcinoma frequently coexists with other histological types of bladder carcinoma. Another theory is that small cell carcinoma originates from Kulchitsky type of neuroendocrine cells which exists within the urothelium and gives rise to neuroendocrine tumors.

Bladder small cell carcinoma is infrequently associated with paraneoplastic syndromes, in contrast to its pulmonary counterpart. The uncommon paraneoplastic syndromes include hypercalcemia, sensory neuropathy and Cushing's syndrome. Our case presented with hypercalcemia.

The typical microscopic features of small cell carcinoma are hypercellularity, geographic necrosis, and salt and pepper type of nuclear chromatin, crush artifact and increased mitosis. In the differential diagnosis lymphoma, poorly differentiated urothelial carcinoma and metastatic small cell carcinoma from another primary site such as lung and prostate should be considered. On the basis of morphology and immunohistochemical profile the differentials of lymphoma and poorly differentiated urothelial carcinoma can be excluded. In view of the almost identical morphology and immunoprofile the distinction between primary and metastatic small cell neuroendocrine carcinoma is impossible. A good clinicopathological and

radiological correlation resolves the contemplation. Since TTF1 can be positive in 40% primary small cell carcinoma, positivity does not necessarily suggest a metastatic lung tumor.

Small cell carcinoma is more frequently admixed with other histologic subtypes. The mixed epithelial component is most commonly conventional urothelial carcinoma with squamous cell carcinoma and adenocarcinoma, which has led to the proposed origin of both tumors suggesting that small cell appearance, may represent dedifferentiation within the urothelial neoplasm. In most reports the authors showed a higher incidence of mixed small cell carcinoma. In Abrahams study, mixtures of small cell carcinoma with transitional carcinoma was present in 70% of cases, while mixtures of small cell carcinoma with adenocarcinoma and squamous carcinoma was present in only 8% and 10% of the cases respectively.² Abenzoza et al reported a similar case of a primary mixed adenocarcinoma–neuroendocrine carcinoma of the urinary bladder.⁹ Tumors with even focal small cell histology show dismal prognosis that is more similar to pure small cell carcinoma than to urothelial carcinoma or to pure tumors consisting of other components therefore warranting a diagnosis as small cell carcinoma.¹⁰

p53 overexpression has been documented in multiple case series on small cell carcinoma of the bladder with the largest series demonstrated a p53 overexpression in 54% (27 of 50) of bladder small carcinoma cases. However no definite correlation between p53 overexpression and poor prognosis was demonstrated, possibly because the overall prognosis for bladder small cell carcinoma is poor regardless of the various clinicopathologic parameters.¹¹

Small cell carcinoma of the bladder is poorly differentiated, presents with muscle invasive disease and

more than 95% of cases present at an advanced local stage.¹² The optimal management of these highly aggressive tumors is not well defined. Therapeutic modalities vary and include transurethral resection, cystectomy, radiation therapy and systemic chemotherapy. Surgical resection is unlikely to be curative unless the tumor is confined to the bladder.

In the metastatic setting the most commonly used regimen for small cell carcinoma of bladder is Cisplatin with Etoposide. The National Comprehensive Cancer Network guidelines of 2015 recommend resection and chemotherapy, with or without radiotherapy for non-locally advanced tumors, radiotherapy and chemotherapy for loco regional advanced disease and chemotherapy alone for metastatic disease.¹³

Conclusion

Primary small cell carcinoma of the urinary bladder is rare and aggressive tumor. In more than 50% of the cases the diagnosis is at an advanced stage. Small cell carcinoma of the urinary bladder in contrast to its pulmonary counterpart rarely presents with hypercalcemia which was seen in our case and is being presented for this rarity. The origin of the disease is not clearly defined, but the multipotent theory is most accepted. Coexistence of small cell carcinoma of the bladder with other types of carcinoma is common. Immunohistochemistry plays a major role in the diagnosis. Pure small cell shows to have a worsened prognosis than the mixed cell histology. The accurate recognition of these “variant” morphologies is of paramount importance due to the diagnostic dilemma that they may present, as well as prognostic and therapeutic implications these diagnosis may have.

Conflict of Interest: None.

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How to cite this article: Sadiya N, Sezhian N, Ghosh M, Lamech D. A varied morphological spectrum of urinary bladder carcinoma - A rare diagnostic entity. *Indian J Pathol Oncol* 2019;6(2):331-5.