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Primary Small Cell Carcinoma of Urinary Bladder with Review of Literature

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Abstract: ***Small cell carcinoma of the urinary bladder is a rare disease. It shares similarities in age of presentation, sex preference, symptoms, and appearance with conventional urothelial carcinoma. However, it is significantly more aggressive in its biological behaviour even when compared at similar stages. Metastasis is common at the time of diagnosis and prognosis is poor. Histologically, it resembles small cell carcinomas found in the lungs and other organs, though it exhibits lower reactivity to typical neuroendocrine markers. This cancer presents significant diagnostic challenges as its clinical presentation mimics other bladder tumours. We present an interesting and uncommon case, initially misdiagnosed as transitional cell carcinoma in the transurethral resection specimen. This case report presents a rare instance of Small cell carcinoma of the urinary bladder in a 56 - year - old male, shedding light on the diagnostic journey. The patient presented to the urological department with haematuria, dysuria, and hypogastric pain. Initial investigations revealed a bladder mass. A computed tomography (CT) scan was used to evaluate local and distal extension. A comprehensive histopathological examination, including immunohistochemistry, confirmed Small cell carcinoma of the urinary bladder.***

Keywords: Small cell carcinoma, Urinary bladder, neuroendocrine tumor

1. Introduction

Bladder cancer primarily consists of urothelial carcinoma which constitute over 90% of the cases. Apart from urothelial carcinomas, non - urothelial epithelial malignancies of the urinary bladder include squamous cell carcinoma, adenocarcinoma and neuroendocrine tumours. Neuroendocrine tumours represent a much smaller subset of bladder malignancies and are categorized into two main types: carcinoid tumours and neuroendocrine carcinoma. Neuroendocrine carcinoma is further divided into small cell carcinoma and large cell neuroendocrine carcinoma, although the latter is extremely rare in the bladder.

2. Case Presentation

A 56 year old male patient presented to the outpatient department with complaints of haematuria, dysuria, and hypogastric pain. Patient was a chronic smoker since last 20 years. The past history was significant as the patient had been operated for bladder carcinoma two years earlier. It was classified as high grade urothelial carcinoma without muscular invasion on microscopy. Post op scans showed no residual disease.

Now, two years later, Contrast Enhanced CT also showed a 60X57X40 mm soft tissue density mass showing contrast enhancement at infero - lateral wall and base of urinary bladder with loss of fat planes to seminal vesicles and intraluminal extension. MRI also corroborated the findings suggesting a possibility of recurrent lesion. On cystoscopy a 6x6cm lesion with internal vascularity in left inferolateral wall was identified in the urinary bladder.

Cytological urine analysis was unsatisfactory and showed inflammatory cells only.

Initial TURB biopsy was misdiagnosed as urothelial carcinoma. A repeat TURB biopsy was done and revealed tumour cell nests having hyperchromatic pleomorphic nuclei with minimal amount of cytoplasm. Brisk mitotic activity was seen with areas of necrosis. Tumour was found to be invading into lamina propria. Deep muscle (Detrusor muscle) was not identified in the biopsy submitted. Overall histomorphological features were in favour of poorly differentiated high grade carcinoma. Possibility of small cell carcinoma was suggested.

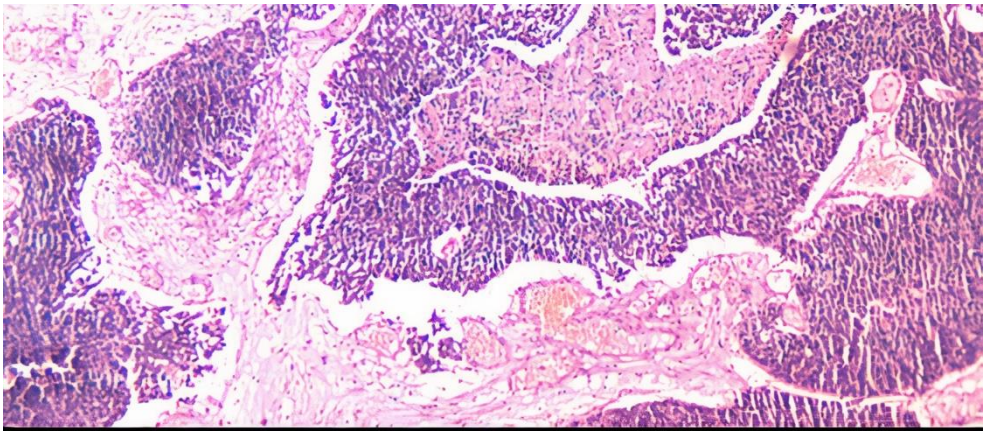

Figure 1: 10x section shows tumour cells arranged in solid sheets, trabeculae and complex fused papillary formation

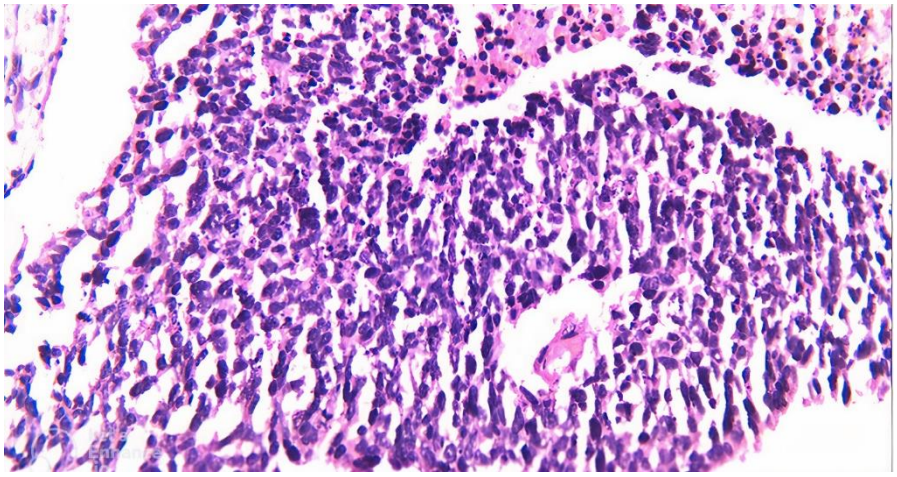

Figure 2: 40X shows tumour cells having round to oval elongated nuclei with hyperchromasia, nuclear overlapping, high N: C ratio and minimal cytoplasm. Mitotic activity is brisk.

IHC was performed for exact categorization which revealed tumour cells showing diffuse membranous and dot like positivity for Pan CK, diffuse and strong positivity for Synaptophysin and focal positivity for CK7 and TTF - 1. Tumour cells were negative for CK20 and GATA - 3 confirming the diagnosis of small cell carcinoma.

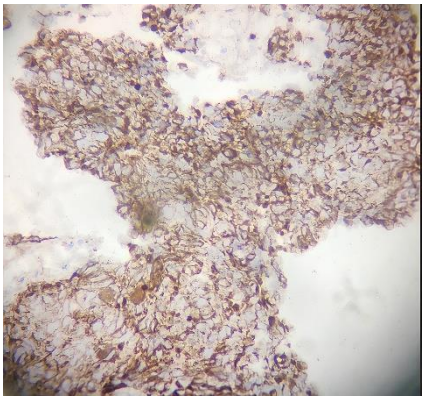

Figure 3: Pan CK showing dot like positivity on Immunohistochemistry

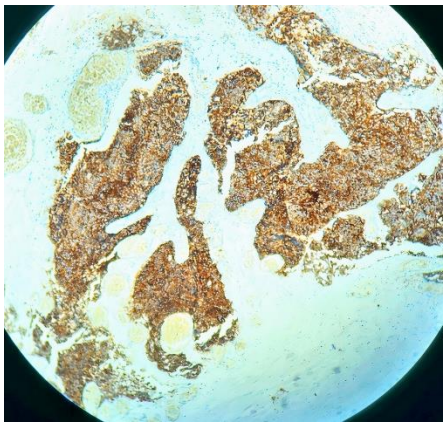

Figure 4: Diffuse and strongly positive synaptophysin

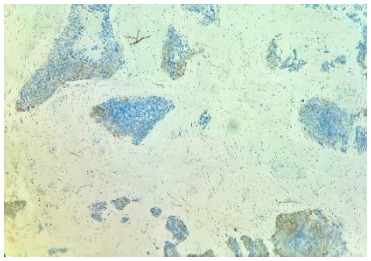

Figure 5: Focally positive CK7

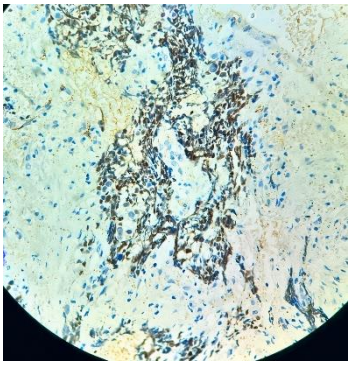

Figure 6: Focally positive TTF1

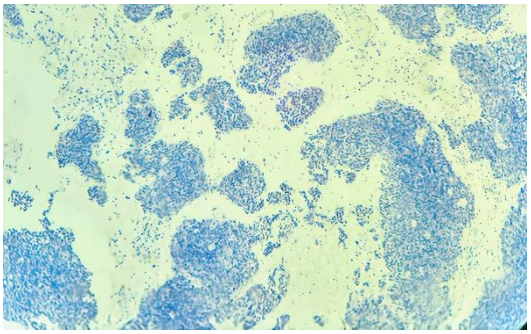

Figure 7: GATA 3 was negative on IHC

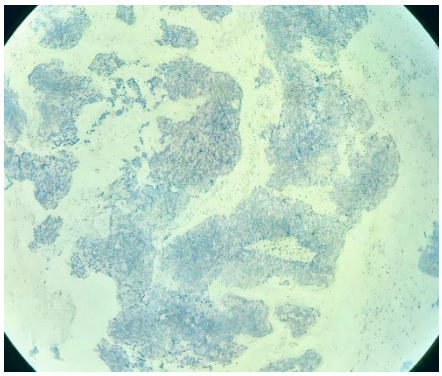

Figure 8: CK20 was negative on Immunohistochemistry

Differential diagnosis

1) Primary small cell carcinoma of urinary bladder
2) Metastasis of small cell carcinoma lung

Imaging did not reveal any lesion in the lungs, so a metastatic small cell carcinoma was ruled out, and a diagnosis of primary small cell carcinoma was arrived at.

3. Literature Review on Small Cell Carcinoma of the Urinary Bladder

Epidemiology

Small cell carcinoma (SmCC) of the urinary bladder is a rare and aggressive form of neuroendocrine tumour that was first reported by Cramer et al.1 in 1981. It constitutes less than 1% of all bladder cancers [3; 8; 9; 10; 27; 28; 31]. SmCC of the urinary bladder predominantly affects older adults, with a male predominance. The age at diagnosis is typically in the sixth to seventh decade of life. [3; 8; 9; 11; 14; 15]

In Indian context, two retrospective studies were found, Nabi et al., 2001[13] studied 11 patients and found the mean age of presentation to be 60 with a male preponderance and Ram et al., 2021[30] corroborated with 60 as median age of presentation with a male preponderance of 80%.

Pathogenesis

The pathogenesis of SmCC is not fully understood, but it is believed to arise from neuroendocrine differentiation of urothelial cells [1; 10]. Unlike conventional transitional cell carcinoma, SmCC exhibits distinct genetic and molecular characteristics. Key genetic alterations have been identified, particularly in the TP53 and RB1 tumour suppressor genes, which are frequently mutated in these tumours [22; 23; 24]. These genetic changes may drive the aggressive behaviour observed in SmCC, leading to rapid growth and metastasis. Additionally, the microenvironment of the bladder may play a role in tumour development, with inflammatory processes contributing to tumorigenesis.

4. Clinical Features

Gross haematuria has been the most prominent symptom; other symptoms, such as dysuria, pelvic pain, or even paraneoplastic syndromes, are less frequent. [1; 3; 6; 12; 13; 33; 34; 36]. Choong et al., 2005[3] and Helpap et al., 2002[12] reported that most of the cases had muscle invasion when the diagnosis was made. Metastatic diseases ranged, depending on the bibliography, from 28 to 67%. The most common sites of metastatic disease are the lymph nodes, liver, bone, lung, and brain. [6; 12; 13; 33; 34; 3]

5. Diagnosis

Diagnosis of SmCC of the bladder relies on a combination of histopathological examination and immunohistochemical analysis. Imaging studies, including computed tomography (CT) and magnetic resonance imaging (MRI), play a crucial role in staging the disease and assessing for distant metastases. Positron emission tomography (PET) scans may also be utilized for further evaluation. Cystoscopy is the primary diagnostic tool, allowing visualization of the bladder mucosa and targeted biopsy. Cystoscopy often reveals abnormal findings such as masses or tumours that appear infiltrative rather than well - defined, which is characteristic of this aggressive cancer type. Lesions may be irregularly shaped and can present with ulceration or necrosis. [3; 15; 21; 25]

- **Histological examination -**

Morphology of small cell carcinoma of urinary bladder is similar to pulmonary small cell carcinoma.

Uniform small cells (generally larger than lymphocytes) or intermediate cells with hyperchromatic, dense, round, or oval nuclei with marked nuclear pleomorphism and generally absent nucleoli, ‘salt and pepper’ chromatin and sparse cytoplasm are seen. Frequent mitoses (>10mitotic figures/ 10 high power fields) is seen. Cells are arranged in sheets or irregular nests. Large areas of necrosis are commonly seen. Indian file pattern and rosette formation may be seen. Invasion of small vascular channels is commonly present [19; 32; 36]

- **Immunohistochemistry -**

Majority stain for at least one epithelial marker like epithelial membrane antigen, broad - spectrum cytokeratin and at least

one or two neuroendocrine markers (neuron - specific enolase, synaptophysin, chromogranin). [7; 10; 11; 29]
CAM5.2 staining in distinctive punctate perinuclear pattern (compared to membranous pattern in urothelial carcinoma)
TTF1 expression can be seen in both small cell bladder and lung. [20]

IHC may also be used to assess for the presence of p53 mutations, which can provide insight into the tumour's aggressiveness and potential response to treatment.

6. Treatment

Treatment for SmCC of the urinary bladder typically involves a multimodal approach. Due to the tumour's aggressive nature, chemotherapy is the cornerstone of treatment. The regimen commonly employed is a platinum - based combination, such as cisplatin and etoposide, which has shown some efficacy in treating small cell carcinomas. In cases where the tumour is localized, radical cystectomy and pelvic lymphadenectomy may be considered. However, the high rate of metastasis often makes surgical resection less effective as a primary treatment strategy.

Radiation therapy may be used in combination with chemotherapy, particularly in cases where the disease is not amenable to surgery or in palliation of symptoms. Despite aggressive treatment, the prognosis remains poor, with a high rate of recurrence and metastasis.

7. Prognosis

The prognosis for SmCC of the bladder is generally unfavourable compared to other types of bladder cancer [9; 11; 35]. The median overall survival ranges from 8 to 18 months, depending on the stage at diagnosis and response to treatment. Factors influencing prognosis include the extent of local invasion, presence of metastases, and the patient's overall health. Recent studies suggest that early diagnosis and aggressive treatment may improve outcomes, but survival rates remain lower than those for more common bladder cancers.

8. Conclusion

Small cell carcinoma of the urinary bladder represents a challenging and rare malignancy with distinct clinical and pathological characteristics. Although advancements in diagnostic and therapeutic modalities have been made, the aggressive nature of this cancer and its propensity for early metastasis continue to pose significant treatment challenges. Continued research into more effective treatment strategies and better understanding of the molecular mechanisms underlying this disease are essential for improving patient outcomes and survival rates.

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