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Small Cell Neuroendocrine Carcinoma of Bladder

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Abstract **Case Report**

Being a very rare histopathological type, neuroendocrine tumors are rather aggressive tumors that are usually diagnosed at an advanced stage. Neuroendocrine bladder tumor represents less than 1% of all bladder cancers. Though diagnosed in similar age period of 6th to 8th decade like urothelial carcinoma, its histopathological features and its poor prognosis are apart and rather similar to the small cell cancer of the lung. In this case report, we present a case of high-grade small cell neuroendocrine carcinoma of bladder in an elderly man.

Keywords: Bladder, cancer, neuroendocrine, small cell, TUR-BT.

INTRODUCTION

Being a very rare histopathological type, neuroendocrine tumors are rather aggressive tumors that are usually diagnosed at an advanced stage [1-4]. Neuroendocrine tumors have been commonly reported in the lungs, the small intestine, but very rarely in the urinary system [3]. Neuroendocrine bladder tumor represents less than 1% of all bladder cancers [1, 2]. Though diagnosed in similar age period of 6th to 8th decade like urothelial carcinoma, its histopathological features and its poor prognosis are apart and rather similar to the small cell cancer of the lung [1-4].

In this case report, we present a case of high-grade small cell neuroendocrine carcinoma of bladder in an elderly man together with radiological imaging and histopathological pictures.

CASE REPORT

Eighty-four year old male patient administered to emergency service with gross macroscopic hematuria. His medical history included a recent (one-year ago) left inguinal radical orchiectomy with the histopathological diagnosis of Leydig cell tumor (pT1a). Patient was under follow-up for Leydig cell tumor without any further chemotherapy or radiotherapy. He was non-smoker and taking combined medical therapy for LUTS suggesting BPH. Magnetic resonance imaging of abdomen, performed upon admission, revealed mass lesion that had almost completely filled the bladder and was extending towards the fatty tissues in the left perivesical area (Figure 1). FDG-PET study revealed a parenchymal metastatic nodule in the medial segment of the middle lobe of the right lung and metastatic lymph nodes in the left external and internal iliac region and left paraaortic regions. Patient's one-year old imaging modalities done for staging of testicular Leydig cell carcinoma were re-visited. The mass as well the metastases, missing in one-year old imaging studies, were confirmed to develop rapidly within almost one-year. In cystoscopy, solid tumoral mass lesion was found to fill almost all bladder walls. Transurethral resection was performed for histopathological diagnosis. The histopathological evaluation according to latest W.H.O. 2022 classification resulted high grade, small cell neuroendocrine carcinoma (pT2) with focal carcinoma in situ [7]. It was reported to have no conventional urothelial carcinoma with immune-histological Ki-67 proliferation rate of >90% (tumor cells were INSM-1 (+), synaptophysin (+), chromogranin-A patchy (+), AE1/AE3 (-) punctate (+), p63 patchy (+), GATA-3 focal (+), CK7 (-), CK20 (-), TTF-1 (-), p53 wild type were observed) (Figure 2). The patient was postoperatively referred to intensive care unit

of chest disease because of postoperative acute respiratory distress syndrome (ARDS). The patient died of ARDS approximately 7 weeks after TUR-BT.

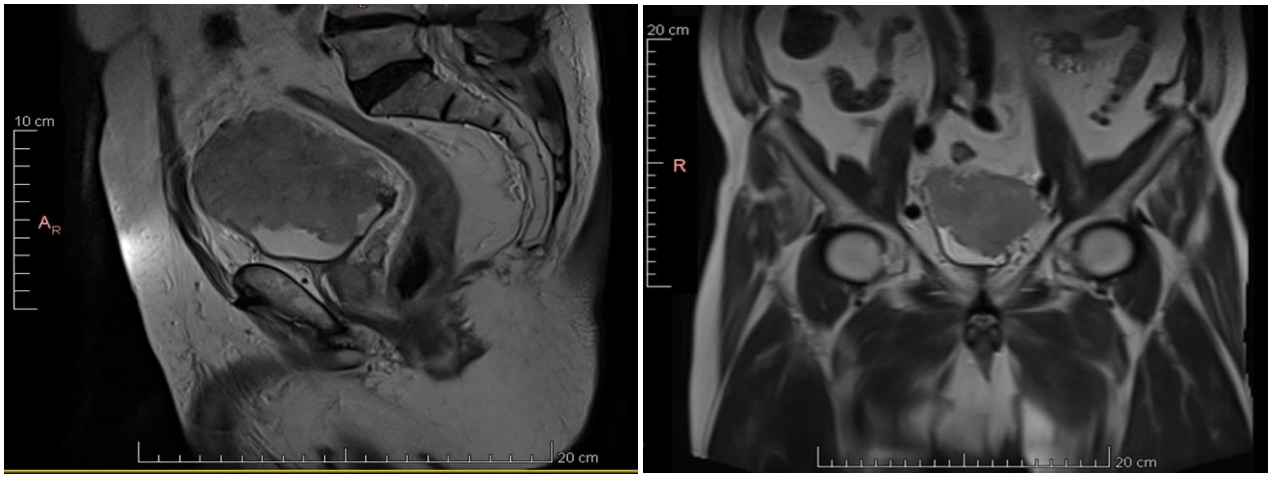

Figure 1: Magnetic Resonance Imaging (MRI) scans (Siemens 1.5T, Magnetom, Erlangen, Germany) demonstrated huge mass involving especially the superior wall and the other walls of the urinary bladder (T2W images, sagittal plane on left; Coronal plane on right)

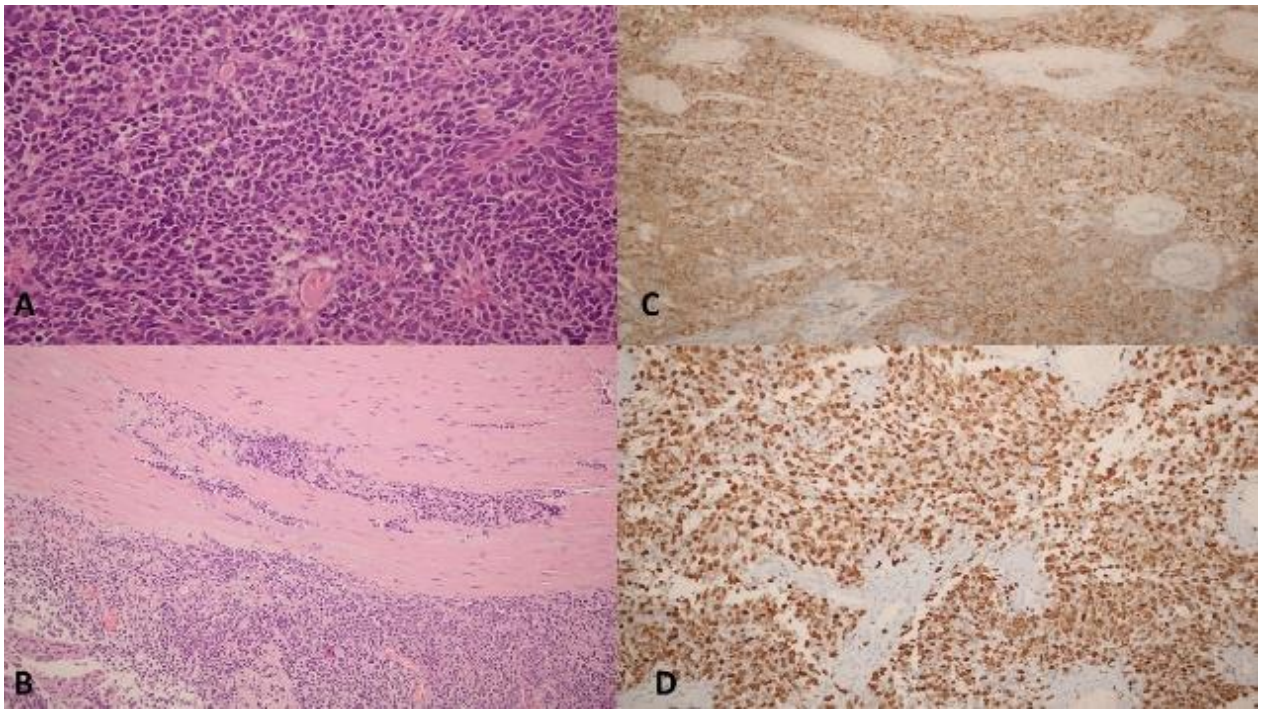

Figure 2: (A). **Photomicrograph showing tumor cells with high nucleocytoplasmic ratio, nuclear molding, indistinct nucleoli and high mitotic activity arranged in diffuse sheets, H&E 400X;** (B). **Infiltration of the muscularis propria by neoplastic cells, H&E 200X** (C). **The tumor cells show diffuse cytoplasmic granular positivity for synaptophysin, 400X**; (D). **The Ki-67 proliferation index of the tumor is very high, 95%, (400X).**

DISCUSSION

Small cell neuroendocrine carcinoma of the bladder is a rare, aggressive cancer that accounts for an estimated less than 1% of bladder cancers [1, 2]. However, it is uttermost important to note that these referenced studies are three-decade old, during which many histopathological diagnostic criteria and nomenclature changes have been done. Of these changes, the latest version is 2022 WHO [3]. Nevertheless, these historical studies have large number of cases reported together with one published in 2001 [1, 2, 4]. One of these, performed in a single institution of 8-year data, revealed six cases of either pure or urothelial carcinoma-associated oat cell carcinoma among 552 bladder cancer patients [1]. The other one including multi-institutional pathological archives' data, revealed 18 cases of either pure or urothelial carcinoma-associated oat cell carcinoma among 3778 bladder cancer specimens [2]. Patients with small cell neuroendocrine carcinoma tend

to have higher T stages ($\geq pT_2$) [1, 2, 4]. As a summary of these studies with larger number of cases, the common symptom was hematuria, the median tumor size was 5 cm [2-10 cm], the median age was 68 years [35-84 years], female to male ratio was 6/99, and death rate was 88.2% within median 12 months [1-34 months] [1, 2, 4].

Apart from extensively revised histopathological, some relevant case studies in literature give data about just neuroendocrine carcinoma of bladder without defining large or small cell subtypes [5]. In the new histopathological description, pathologists make use of hormones, enzymes and keratins involved in functional and structural correlation with traditional biomarkers of neuroendocrine origin and differentiation, INSM1, synaptophysin, chromogranin and somatostatin receptors (SSTRs) [3]. Especially, using immunohistochemically markers, including cytoplasmic chromogranin a, synaptophysin positivity and 'dot-like' cytokeratin positivity are important for diagnosis. Thyroid transcription factor-1 (TTF-1) positivity was reported in 25-39% of bladder small cell carcinoma, limiting its use in this regard [6]. Likewise, in our case, synaptophysin, chromogranin A and INSM-1 were positive together without a secondary histopathological type, and TTF-1 was negative.

As well, association of metachronous or synchronous secondary malignancies have rarely been associated with neuroendocrine tumors [7, 8]. In one report, two cases with colon cancer and rectum neuroendocrine cancer have been detected in a series of 111 patients with bladder neuroendocrine tumor [7]. In another study, 10-year records of a single institution have revealed 12 patients with primary bladder small cell neuroendocrine carcinoma, they were found together with other tumor types such as high-grade urothelial carcinoma and squamous cell carcinoma of the bladder in 8/12 of the patients. In addition, in five of the six cases who underwent cystoprostatectomy there were ISUP I or ISUP II prostate adenocarcinoma [8]. Our patient has undergone radical orchiectomy one year ago with resulted pathology of testicular Leydig cell carcinoma. These examples together with our case may suggest an underlying genetic susceptibility for synchronous/metachronous cancer associated with neuroendocrine bladder cancer.

These small cell neuroendocrine tumors tend to have either synchronous or de novo metastases during follow up, mainly to brain, lymph nodes, liver, lung and bone [9-13]. In our case, metastases to lung parenchymal nodules and iliac lymph nodes were detected.

Though its high mortality rate, some young cases with metastatic iliac lymph nodes have been reported to live disease free for at least 12 months after radical cystoprostatectomy combine with adjuvant chemo-radiotherapy [14]. Our case was rather elderly with additional comorbiditie and he died due to ARDS six weeks after TUR-BT.

Primary small cell neuroendocrine carcinoma of the bladder is a rare urological tumor with high aggressiveness and poor prognosis. Other types of cancer that may develop synchronously or metachronously and the high tendency of metastatic disease should also be kept in mind. Both treatment and pathophysiology have not been fully elucidated. In the particular case we presented, although death occurred due to respiratory distress and no additional treatment could be given to the patient after TURBT, radical cystectomy after neoadjuvant chemotherapy might be considered as treatment, if possible, in suitable patients.

Conflict of Interest: None declared.

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