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SMALL CELL CARCINOMA OF THE URINARY BLADDER; 3 CASES REPORTED FROM KING FAHAD SPECIALISTS HOSPITAL, KINGDOM OF SAUDI ARABIA

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Abstract:
Small cell carcinoma of the bladder is an extremely rare malignant growth. Its incidence accounts for what is less than 1% of all the primary urinary bladder carcinomata and it should be considered and treated as metastatic disease, even if there is no radiologic evidence of disease outside the bladder. The etiology of this disease is unclear but a theory proposes that small cell carcinoma of the bladder originates from multipotent stem cells and the coexistence of small cell carcinoma of the bladder with other types of bladder malignancies, such as transitional cell carcinoma supports this theory. Three cases all shared hematuria in their presentation. After further investigation, all were diagnosed with small cell carcinoma of the bladder, with and without other types of malignancies and were managed accordingly. The first underwent chemotherapy which consisted of cisplatin/etoposide and palliative radiotherapy. He was issued a DNR later. The second underwent Trans Urethral Removal of Bladder Tumor (TURBT), and chemo-radiation as definitive treatment that took 8 cycles of (cisplatine + etoposide + radiotherapy). Patient was well and cancer-free after 6 years of follow up. The third patient was treated with radical cystectomy, palliative radiation to brain metastases, Androgen Deprivation Therapy (ADT), as well as chemotherapy (goserline + nivolumab) from November, 2018 and until the current moment.Due to the low incidence of small cell bladder carcinoma, there are no clinical data based on prospective case control studies, therefore, more research is necessary to analyse the best plan for its treatment.

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INTRODUCTION

Bladder cancer is the 9th most common cancer worldwide, with 430,000 cases newly diagnosed in 2012[1]. Bladder cancer is the 13th most common cause of death, accounting for 188,000 deaths worldwide (2015)[2]. The worldwide prevalence particularly is higher in men than women[3], and the histological cell type of bladder cancer is very geographically dependent. Urothelial cancer is the most common. In North America and Europe, 95% to 97% of cases essentially are urothelial carcinoma; in Africa 60% to 90% are urothelial and 10% to 40% are squamous cell; and Egypt has the highest rate of squamous cell carcinoma because of the endemic infections with Schistosoma species[4].

The majority (95%) of bladder malignant tumors are transitional cell carcinoma. The other 5% are squamous cell carcinoma, adenocarcinoma, sarcoma, small cell carcinoma (SCC), and secondary tumors from other malignancies elsewhere in the body[5].

Small-cell carcinoma is a type of highly aggressive tumors that arises mainly in the lung, as well as other organs in the body such as the prostate, the cervix, the urinary bladder, as well as the gastrointestinal tract. Small cell carcinoma shows high growth rate and early development of metastases. Small cell carcinoma of the bladder accounts for much less than 1% of all primary bladder tumors and it should be considered and treated as metastatic disease, even if there is no radiologic evidence of disease outside the bladder.

Small cell carcinoma of the bladder (SCCB) is considered one of the Neuroendocrine turmors (NETs). Neuroendocrine tumors can arise from any type of epithelial tissue, but they arise more frequently from epithelial tissue with abundant of enterochromaffin cells. Since the respiratory tract develops embryologically from a bud from the gastrointestinal track, the lungs are also a major site for neuroendocrine tumors to grow.
Very small amount of chromaffin cells are found in the prostate and the urinary bladder thus explain the very small prevalence of small cell carcinoma arising from the urinary bladder[6]. In 2008, cases of bladder malignancies in the United States of America were 68,810 per year, where only 0.5-1% of them were small cell carcinoma[7]. Similar to most bladder carcinomata, small cell carcinoma also show more predominance in males with male:female ratio of 3:1 and it affected Caucasian populations 10 times more than non-Caucasians (10:1)[8].

The etiology of this type of cancer is unclear. A theory proposes that small cell carcinoma of the bladder originates from multipotent stem cells. The coexistence of small cell carcinoma of the bladder with other types of bladder malignancies, such as transitional cell carcinoma also supports this theory.

Another theory proposes that this type of growth is explained by the field effect in cancer, also known as field cancerization, which was introduced by Slaughter et al. in 1953[9], as carcinogens yield changes in the cells of the urothelial lining of the bladder and causes tumors. This is supported by the association of smoking with the incidence of the malignancy[10, 11].

Small cell carcinoma is also evident to occur in the prostate (SCCP), which is a rare tumor accounting for only 1% of all prostatic malignancies. Small cell carcinoma of the prostate is usually detected at an advanced stage as a metastasis from oat-cell carcinoma (small cell carcinoma of the lung)[11]. Although it is rare (0.05% to 0.5%), small cell carcinoma from the prostate is also evident to have metastasized to the brain, which has been reported in the case study of Erasmus et al. where a patient with prostatic small cell carcinoma developed symptomatic brain metastases[12].

Clinical features of small cell carcinoma of the bladder are similar to the clinical features of bladder transitional cell carcinoma which are due to the presence of a mass.

The most common presenting symptom of small cell carcinoma of the bladder is painless gross hematuria; however, local irritation and pain are relatively frequent. Choong et al. reported that 68.2% presented with painless hematuria. Choong mentioned other symptoms that vary in frequencies which include dysuria, urethral obstruction, urinary tract infections, nocturia, paraneoplastic syndromes, weight loss and abdominal pain. At transurethral resection the mass is indistinguishable from urothelial carcinoma, and resection is required to make a histologic diagnosis[13, 14].

The histopathology of small cell carcinoma of the bladder is almost identical to small cell lung carcinoma. Thus, the same criteria established by the WHO classification system are referred to for diagnosis. The small cell carcinoma of the bladder appears, under light microscopic examination in

histological slides stained with hematoxylin and eosin, as small tightly packed cells with few (scanty) cytoplasm which contains few amount of organelles. The nuclei appear pyknotic round to oval in shape. The cells show relatively high rate of mitosis and the majority of reported cases had necrotic figures[15]. High incidence of mixed small cell carcinoma of the bladder have been reported in different studies [15, 16, 17, 18, 19, 20, 21, 22, 23].

In the study of Abraham, mixtures of small cell carcinoma with transitional cell carcinoma was reported in 70% of the cases. However, mixtures of small cell carcinoma with other types of bladder cancers such as adenocarcinoma and squamous cell carcinoma were present in only 8% and 10% of the reported cases, respectively[15].

The immunohistochemistry of small cell carcinoma of the bladder has a major role for its diagnosis by staining the components of the tumor by antibody markers. Those antibody markers target the neuro—specific enolase (NSE), chromogranin, synaptophysin, cytokeratin, serotonin, C-KIT, and EGFR. [15, 24, 25, 26, 27, 28]. Neuron-specific enolase, with the frequency of 88.5%, has expressed most intense cytoplasmic staining, followed by synaptophysin and chromogranin with frequencies of 72.4% and 50%, respectively[24, 25].

Small cell carcinoma of the bladder is responsive to chemotherapy and radiotherapy. However, the prognosis of this pathology remains poor, specially in patients of pure cell carcinoma[6].

CASE REPORT:

Three cases were presented to King Fahad Specialists Hospital (KFSH) in Dammam, Kingdom of Saudi Arabia as the following;

A 66-years old male presented in January, 2012 with Diabetes Mellitus, Hypertension, dyslipidemia, with history of 2 months of painless terminal hematuria in addition to anorexia, and significant weight loss. Cystoscopy performed in January 22nd, 2012 shows small cell carcinoma of the bladder with invasion of muscularis propria. CT scan on the chest, abdomen and pelvis showed lung and liver metastases. In January 29th, 2012, patient was started on chemotherapy cisplatin/etoposide. Patient then started to complain from back pain. MRI showed multi-lytic lesions of the dorsal spine. Palliative radiotherapy was started in February 11th, 2012 and taken 10 fraction. Patient completed 3 sessions of chemotherapy in March of the same year. Patient then was sent for re-evaluation by CT imaging to study tumor progression in bone metastases, MRI of the brain showed metastases, palliative radiation given and patient was following with medical oncology. In September of 2012, patient was in terminal stage and was issued DNR.

In May, 2012, a 56-years old female, with previous history of asthma, presented with hematuria that started 2 months back. CT scan done in another hospital to reveal a urinary bladder mass that measures 3 x 3 cm with few regional lymph nodal enlargements. Trans Urethral Removal of Bladder Tumor (TURBT) was done and showed invasion of muscularis propria with suspicion of small cell carcinoma. Patient was evaluated with CT, PET/CT, and MRI scans that showed multiple masses in the urinary bladder and involvement of the anterior cervical wall with few regional lymph nodes T3N1M0.

Patient underwent chemo-radiation as definitive treatment which included eight cycles of (cisplatine + etoposide + radiotherapy) started in June, 2012 and was completed by October, 2012. In August, 2012, MRI of the abdomen, pelvis and brain show resolution of the previously noted malignancies and revealed no brain metastases. Biopsy was obtained and cystoscopy was run to come back negative for malignancy in March, 2013. Patient is following with imaging every 6 months period since tumor protocol no recurrence of the disease, last follow up was in April, 2018. Patient is well and disease free.

In February, 2018, a 61-years old male with hypertension, good general status and performance was presented with hematuria with clots. He was evaluated with CT scan and he was diagnosed with urinary bladder mass that was measuring 5.3 x 3 x 4 cm with enlarged pelvic lymph nodes. Bimanual exam showed prostate to be hard in consistency. Trans urethral removal of bladder tumor was done and showed Ta high grade urothelial bladder carcinoma, PSA 46. Patient was referred to King Fahad Specialists Hospital and CT imaging was redone and revealed the presence of a bladder mass that measures 6 x 2.5 cm and enlargement of the external and common iliac lymph nodes on both sides. In April, 2018, Transrectal Ultrasound-Guided (TRUS) biopsy from the prostate revealed prostatic adenocarcinoma Gleason (4 + 5) 9. Check cystoscopy and biopsy showed another pathology small cell neuro-endocrine differentiation as well as papillary urothelial carcinoma Ta high grade. In May, 2018, bone scan tested negative, case was discussed in tumor board and recommendations of chemotherapy for bladder carcinoma and Androgen deprivation therapy (ADT) for prostate carcinoma

followed by surgery agreed upon and patient was started on Cisplatin + Etoposide for 4 cycles, and patient started Flutamide followed by Goserline (PSA 72). In August, 2018, CT scan of the brain, chest, abdomen and pelvis showed no brain, chest nor liver metastases, as well as resolution of the neuroendocrine small cell bladder tumor. Enlarged prostate newly developed aorto-caval lymph node and stable bilateral external and common iliac lymph nodal enlargements. No suspicion of bone metastases. In October, 2018, patient underwent open radical cysto-prostatectomy with ileal conduit and extensive lymph node dissection. Histopathology of the prostate revealed acinar adenocarcinoma T2N0, Bladder T0. 0/34 lymph nodes were positive for malignancy. In November, 2018, patient presented to the ER with focal seizure in the left side and weakness in the lower limbs. MRI was run on the brain, cheast, abdomen, and pelvis and revealed multiple brain metastases. No metastases or recurrence nor lymph nodal enlargement was seen in the chest, abdomen or pelvic region scans. Patient given palliative radiation for the brain and ongoing Androgen Deprivation Therapy (ADT) and chemotherapy (goserline + nivolumab) since last November.

DISCUSSION:

Small cell carcinoma is an extremely rare malignant growth in all parts of the urinary system and tract. Its incidence accounts for what is less than 1% of all the primary urinary bladder carcinomata [14, 21]. In a study by Choong et al., it was found that only 44 out of 8,345 were diagnosed with small cell carcinoma of the bladder accounting for about 0.53% of all reported cases[14]. Also, in the study of Blomjous et al., 18 out of 3,778 cases were diagnosed with small cell bladder carcinoma accounting for 0.48% only.

There is a significant increase in the incidence of this type of tumor in males (male to female ratio is 5:1), and taking 67 years as an average age of onset for small cell bladder carcinoma[17, 29]. Symptoms are generally similar to the symptoms of transitional cell carcinoma of the urinary bladder and cases are mostly presented with painless hematuria, which occurs in 90% of all cases. Dysuresia, urinary obstruction, chronic pelvic pain and urinary tract infections were reported in some cases but they are of less frequency than hematuria[30].

Diagnosis of small cell carcinoma of the bladder depends mainly on the pathology reports and the immunohistochemistry of the Trans Urethral Removal Bladder Tumor (TURBT) specimens[31]. However, preoperative urine cytology might help with the diagnosis as Takada et al. reported that 29 out of 43 (67.4%) had class IV or V urine cytology[32].

In the present cases, they were all presented with hematuria with and without other symptoms (as anorexia and loss of weight). After further investigation, all were diagnosed with small cell carcinoma of the bladder, with and without other types of malignancies and were managed accordingly. The first patient, a 66 years old male underwent chemotherapy which consisted of cisplatin/etoposide and palliative radiotherapy. He was issued a DNR later.

The second case, a 56 years old female underwent Trans Urethral Removal of Bladder Tumor (TURBT), and chemo-radiation as definitive treatment that took 8 cycles of (cisplatine + etoposide + radiotherapy). Patient was kept on follow up every six months period for full six years and in April, 2018, patient was well and was completely cancer-free.

The third patient, 6a years old male was treated with radical cystectomy, palliative radiation to brain metastases, Androgen Deprivation Therapy (ADT), as well as chemotherapy (goserline + nivolumab) from November, 2018 and until the current moment. Table 1 summarizes the patients' age, gender, presentation, management, and outcome.

There is no standard treatment for small cell carcinoma of the bladder since it is extremely rare, but treatment options of it include a variety of chemotherapeutic regimens that have been used, but therapy with carboplatin or cisplatin and etoposide is the current treatment of choice[14]. It is common to have a complete response from initial chemotherapy; however, clinical relapse occurs in more than 80% of patients and despite the fact that chemotherapy, mainly cisplatin, is showing promising results, the majority of patients develop metastases that are life threatening and die[33]. It is not uncommon to see small cell carcinoma admixed with other histological types of bladder cancer, including urothelial, adenocarcinoma, and squamous cell cancer[15].

Although chemo-radiation therapy is the primary treatment for small cell carcinoma of the bladder, experience combining chemotherapy with radical cystectomy for primary small cell cancers of the bladder has shown equal, or perhaps better, local control and disease-free survival than found with chemo-radiation[20]. And since chemotherapy is showing high efficacy against metastatic small cell carcinoma, palliative radiotherapy is reserved for the management of symptomatic brain metastases,

symptomatic bone metastases and spinal cord-compressing tumors. A recent study found that symptomatic brain metastases from small cell carcinoma of the urinary bladder are less likely to occur than those from small cell lung carcinoma[34] and therefore it is not recommended to undergo prophylactic brain irradiation in patients with small cell carcinoma of the bladder. However, with 5-year cancer-specific survival rates of 16% to 18% with chemo-radiation or chemotherapy and radical cystectomy, respectively, the primary method to improve survival will be more effective systemic therapy[33, 35, 36].

Case No.	Age (years)	Gender	Presentation	Management	Outcome
1	66	Male	2 months of painless terminal hematuria in addition of anorexia and weight loss. Diagnosed with small cell carcinoma of the bladder on January, 2012.	Chemotherapy which consisted of cisplatin/etoposide. Palliative radiotherapy.	Management from January to September, 2012. DNR was issued in September, 2012.
2	56	Female	Case presented with hematuria. Referring hospital reported 3 x 3 cm bladder mass. Diagnosed with small cell carcinoma of the bladder with involvement of the anterior cervical wall with enlargement of few regional lymph nodes.	Trans Urethral Removal of Bladder Tumor (TURBT), chemo-radiation as definitive treatment that took 8 cycles of (cisplatine + etoposide + radiotherapy).	Patient has been on follow up from May, 2012 until April, 2018 every six months. Patient is well with no evidence of recurrence.
3	61	Male	Case presented with hematuria with clots. Diagnosed with small cell bladder carcinoma, as well as prostate adenocarcinoma.	Patient was treated with radical cystectomy. Palliative radiation to brain metastases. Patient is ongoing Androgen Deprivation Therapy (ADT), as well as chemotherapy (goserline + nivolumab) from November, 2018 and until the current moment.	Diagnosed on February, 2018 and still on follow up.

Table (1): Age, gender, presentation, management and outcome of three cases presented at King Fahad Specialists Hospital (KFSH), Saudi Arabia.

CONCLUSION:

Small cell carcinoma of the bladder is a type of rare, highly aggressive malignant tumor of the urinary tract that metastasizes early and has a poor prognosis, with a low degree of differentiation. The diagnosis can be achieved mainly by means of histological examination and immunohistochemical analysis. Comprehensive therapy that combines surgery, radiotherapy and chemotherapy is the main method of treatment of this aggressive disease. Early comprehensive treatment is recommended. Cases should be carefully discussed in details before treatment. Due to the low incidence of small cell carcinoma in the urinary bladder, there are no clinical data based on prospective case control studies, therefore, more research is necessary to analyse the best plan for treatment.

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