Small cell carcinoma of the urinary bladder

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Abstract

Introduction: Presentation of 3 cases of small cell carcinoma of the urinary bladder and analysis of the most important articles in medical literature.

Materials and method: 3 male patients aged 53, 76 and 48 years were admitted in our department. Based on physical examination, imaging, biopsy TUR-BT and histological report they were diagnosed with small cell carcinoma of the urinary bladder.

Results: Patient 1 underwent neoadjuvant chemotherapy, imaging showing regression of the pulmonary metastasis. Partial cystectomy with pelvic lymphadenectomy was performed and 3 months postoperatively he received adjuvant chemotherapy.

Patient 2 aged 76 years underwent TUR-BT with histopathological diagnosis of bladder carcinoma. Partial cistectomy with iliac and obturatory lymph node dissection was performed. The final histopathological report established the diagnosis of small cell carcinoma. 3 months after surgery he developed left cervical adenopathies. He is ongoing adjuvant chemotherapy.

Patient 3 presented with hematuria. Biopsy TUR-BT pointed out small cell carcinoma. We performed an exploratory laparotomy revealed surgical unresectable tumor. Therefore chemotherapy was indicated.

Discussions: Of outmost importance in managing such patients is the right use of diagnostic algorithm. Consequently, the pathologist is the key factor who must suspect this type of lesion and refer to immunohistochemical staining. Also, the oncologist must apply adequate chemotherapy regimens based on the endocrine origin of the tumor.

Conclusions: Neuroendocrine bladder tumors have high aggressiveness, being underdiagnosed or diagnosed in late stages with undefined treatment. It is important to mention the usefulness of chemotherapy followed by radical cystectomy.

Keywords: urinary bladder, small cell carcinoma, treatment

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Introduction

Neuroendocrine carcinoma is a rare type of cancer, accounting for 0.7% of all bladder cancers. The first case was described by Cramer in 1981. Until now, there are approximately 1000 known cases. It is included in the histological neuroendocrine tumors class (along with large cell carcinoma and carcinoid tumors).

The symptoms are determined by the tumor mass and include: hematuria, dysuria, frequency and urinary obstruction, pelvic and abdominal pain.

Stage presentation is locally advanced or metastatic with a more severe evolution when compared to urothelial tumors. The most frequent metastatic sites are lymph nodes, liver, bones and brain (0-40%) with the average 11%.

Pathology

Differential diagnosis is made with poorly differentiated urothelial tumors, poorly differentiated squamous cell carcinomas, lymphomas, limfoepithelial-like carcinomas, plasmocitoid carcinomas, large neuroendocrine tumors, metastasis from pulmonary small cell carcinoma.

Histologically, WHO describes 3 groups of small cell bladder cancers based on microscopic patterns:

(i) Oat cell appearance with small round malignant cell with double the diameter of a lymphocyte, these cells have pyknotic nuclei, round or oval, discrete nucleoli and little cytoplasm
(ii) Intermediate cell type with larger ramified cells, spindle or polygonal. The cytoplasm of these cells is more abundant.
(iii) Mixed forms in which other histological types appear.

Immunohistochemistry – positive reaction to neuronal specific enolase, chromogranin A, synaptophysin.

Imaging

When this diagnosis is taken into consideration a thorough imaging exam must be performed (CT or MRI) including pelvic, abdominal and thoracic scans. Because of the high frequency of metastasis we also recommend cranial MRI. Bone scintigraphy is performed only when the patient is symptomatic.

Regardless of the imaging technique used (CT or MRI) the evaluations usually describe large tumors (frequently larger than 5 cm).

The staging system used is TNM 2010.

We underline the necessity of TUR-BT and histological report (tumor chemosensitivity implies neoadjuvant therapy).

Treatment

The accepted treatment at the moment is multimodal therapy: surgery (TUR-BT, partial cystectomy, radical cystectomy), chemotherapy (adjuvant, neoadjuvant) and radiotherapy.

Materials and Method

Patient PS aged 53, previously diagnosed with bladder tumor by TUR-BT (August 2012 – County Hospital Timis), with histopathological diagnosis of small cell carcinoma pT2G2/G3 was initially treated with 4 series of Gemtabicine and Carboplatine as neoadjuvant chemotherapy. The computed tomography revealed a 4 cm metastasis in the inferior lob of the right lung, reduced to 1 cm after chemotherapy. The patient is admitted in our service for further investigation and treatment.

Clinical examination was within normal range.

Computed tomography revealed an infiltrative right lateral bladder wall tumor with pulmonary metastasis.

Following these investigations the patient benefited from partial cystectomy with safety margins and standard bilateral pelvic lymph node dissection.

Postoperative period was uneventful. The final histopathological report showed a small cell bladder carcinoma staged pT2N0M0G2.

The patient is currently under chemotherapy.

Patient CI aged 76, previously diagnosed with infiltrative bladder tumor by TUR-BT in October 2012, with histopathological diagnosis of urinary bladder carcinoma pT2G3, is admitted in our service for further treatment. The associated cardiac pathology required cardiac pacemaker implantation (second degree AV block type 1).

Computed tomography after TUR-BT described a thickened urinary bladder wall, with pseudodiverticular aspect with a maximum wall thickness of approx. 22 mm, mostly expressed at the level of supero-lateral right wall with contrast enhanced mucosa. The parietal thickening of urinary bladder requires correlation with cystoscopic examination.

Following these investigations, partial cystectomy (T2N0MxG3) was performed with 4 cm safety margins. Postoperative period was uneventful, with a final histopathological report confirming the diagnosis of small cell bladder carcinoma.
Patient HA aged 48, with intermittent hematuria for approximately 1 month, urinary blood clots and imagistic diagnosis (ultrasound, CT) of infiltrative bladder tumor on the left lateral wall and grade IV hydronephro-ureter is admitted in our service for further examination and treatment.

Ultrasound revealed a normal right kidney and stage IV left hydronephrosis with 9mm parenchyma.

Cystoscopic examination found a large, sessile tumor, approx 5/4cm diameter on the left lateral wall, obliterating the left ureteral orifice, having an infiltrative aspect, consequently requiring radical cystectomy.

In June 2013 surgical exploration was performed revealing a large lymph node mass on the level of left obturator canal, surrounding the left iliac vessels, expanding upwards towards left common iliac vessels, with infiltration of left psoas muscle. We perform a left obturatory canal lymph node biopsy. Given the context, we decide to delay the surgical treatment, referring the patient for neoadjuvant chemotherapy. TUR-BT biopsy of the urinary bladder tumor reported small cell carcinoma of the bladder.

Postoperative period was uneventful, the patient being dismissed and referred to oncology department for chemotherapy.

Discussions

A SEER statistics made by Koay between 1991-2005, published in Cancer 2011, shows that for 642 patients with treated small cell urinary bladder cancer, the average survival was 11 months (12-24 months) as opposed to 4-5 months without treatment.

The surgical treatment applied was TUR-BT (55%), partial cystectomy (6,5-13%), radical cystectomy (17-25%), radiotherapy (23-24%) and chemotherapy (37%).

The article concluded that within 70000 new cases of bladder tumors in USA, 500 new cases are to be small cell cancers, so chemotherapy is underutilized.

Another SEER study by Schriieber during 1988-2007, published in the American Journal of Clinical Oncology in April 2013, that included 603 patients with small cell bladder tumor showed an average survival of 12 months.

35.4% of patients were stage IV according to AJCC with an average tumor size of 4 cm (0.2-15 cm)

Survival after TUR-BT was 11 months, after radical cystectomy 21 months and after radiotherapy was 17 months.

No data regarding chemotherapy can be assessed from this study.

Another conclusion refers to chemotherapy that is underutilized.

Anderson MD Center recommends neoadjuvant chemotherapy, followed by radical cystectomy.

An indication of 4 series of chemotherapy is proposed, consisting of Cisplatin + Etoposide alternating with ifosfamide and doxorubicin followed by radical cystectomy and another 2 series of chemotherapy with 5 year survival of 78% ( compared to 36% treated with radical cystectomy alone) (Sieker Radke).

More recently, reports of an average survival of 58 months at 18 patients treated with neoadjuvant chemotherapy followed by cystectomy were also published.

N.Choong, from Mayo Clinic, Rochester Minnesota, in a study comprising 44 patients with small cell urinary bladder cancer diagnosed between 1975-2003 reported 12 patients (27.3%) with stage II, 13 patients (29,6%) with stage III and 19 patients (43,2%) with stage IV. Average survival was 1.7 years. 5 year survival was 63.6%, 15.4% and 10.5% for stages II, III and IV. 6 out of 8 patients with stage II disease were treated by radical cystectomy. 5 patients with stage IV disease had obvious metastasis and underwent chemotherapy. 14 patients previously treated by radical cystectomy, were diagnosed afterwards as T4 or N+ (N1-N3). Only 2 out of 19 patients who underwent adjuvant treatment survived after 5 years. The article concludes that patients with small cell urinary bladder cancer can be treated with radical cystectomy, except those with metastasis (M1), who should be treated with systemic chemotherapy. Adjuvant treatment is not indicated in stage II disease, and should be considered mainly for stages III and IV. It is recommended that chemotherapy should be performed using platinum salts.

Another study, from South California University (Ques) containing 2005 cases of radical cystectomy (between 1971-2004) identifies 25 cases (1,2%) of neuroendocrine cancers (20 with small cells, 5 with large cells). 76% of the patients had lymph node metastasis and 2% liver metastasis.

All patients were treated by radical cystectomy and 14 underwent chemotherapy (1 neoadjuvant and 13 adjuvant)

2 year survival was 30% and 5 year survival was 10%. The author emphasizes the fact that results were better in patients treated by chemotherapy.
Conclusions

Small cell bladder carcinoma is a very aggressive and chemosensitive type of cancer and mainly not diagnosed preoperatively (in Quek's statistics 36% of the cases were not diagnosed by TUR-BT, but on the cystectomy specimen). Because of the small number of cases, the treatment is not clearly defined. The MD Anderson Clinic with the largest experience on this subject, indicates 4 series of neoadjuvant chemotherapy with Cisplatin and Etoposide alternating with Ifosfamide and Doxorubicin followed by radical cystectomy and other 2 series of adjuvant chemotherapy with 5 year survival of 78%, compared to 36% with cystectomy only.

References:
8. Eugene J. Koay, MD, PhD1,2; Bin S. Teh, MD3,4; Arnold C. Paulino, MD3,4; and . Brian Butler, MD3,4 A Surveillance, Epidemiology, and End Results Analysis of Small Cell Carcinoma of the Bladder Epidemiology, Prognostic Variables, and Treatment Trends Cancer 2011;117:5325–33.
9. David Schreiber, MD,* Justin Rineer, MD,w Jeffrey Weiss, MD,*z Andrea Leaf, MD,*Nicholas Karanikolas, MD,* Marvin Rotman, MD, and David Schwartz,MD Characterization and Outcomes of Small Cell Carcinoma of the Bladder Using the Surveillance, Epidemiology, and End Results Database. American Journal of Clinical Oncology, Volume 36, Number 2, April 2013