SMALL-CELL CARCINOMA OF THE URINARY BLADDER: WHERE DO WE STAND?

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Abstract

Small-cell carcinoma of the urinary bladder is a very rare pathology, but with a very aggressive behavior and disappointing prognosis. The literature concerning this type of cancer is scarce and physicians may encounter difficulty trying to manage it. Most articles involve the study of case series, without definite results due to the small number of patients. The present article aims at gathering the most significant articles and results in order to offer a broad perspective on the existing literature concerning this pathology.

Keywords: small cell carcinoma, bladder cancer, neuroendocrine tumor

Introduction

Neuroendocrine tumors (NETs) can arise from any type of epithelium, but more frequently they develop from epithelia rich in enterochromaffin cells, like the gastrointestinal tract. Taking into consideration the fact that the respiratory tract develops from the gastrointestinal bud, the lung is also a frequent localization of NETs.

A very small number of chromaffin cells can be found in the bladder and prostate, thus accounting for an infinitesimal number of NETs of the genitourinary system, and particularly of the urinary bladder.

Small-cell carcinoma of the bladder (SCCB) is a type of NET, along with large-cell carcinoma of the bladder (LCCB) and the carcinoid tumors. Even though SCCB is the most frequent of the NETs of the bladder, its understanding is limited and finding useful resources for physicians may be troublesome.

Epidemiology

Neuroendocrine carcinoma of the urinary bladder is an extremely rare pathology, accounting for only 0.35-0.70% of all bladder cancers, according to Choong et al. [1]. Neuroendocrine carcinoma is further subdivided into small cell and large cell carcinoma, the latter being the rarer of them and with a very scarce literature to help physicians.

According to Shailen [2] citing the Cancer Statistics of the American Cancer Society [3], in 2008 the incidence of bladder cancer was 68810 cases per year in the United States of America, out of which only 0.5%-1% were small-cell carcinoma. Choong et al. report that on a 28-year span at the Mayo Clinic, 8345 patients presented with bladder cancer and 44 of them had primary bladder small-cell carcinoma, meaning 0.53% of all bladder cancers [1]. In an article from 1989, Podesta et al. note that small-cell carcinomas may have been included in the past with high-grade carcinomas and have not been identified as an individual entity [4]. Thus, retrospective studies should be regarded skeptically.

Most studies reveal that there is a male predominance for this type of cancer with a male:female ratio 3:1, with a ratio of Caucasian:non-Caucasian patients of 10:1 [5]. The males affected are more likely to be in their sixth or seventh decade with a history of smoking (50-70% - Shailen), data that superpose with those of urothelial bladder cancer [2].

Choong et al. note that the most common cause for presentation was painless macroscopic hematuria (68.2%) [1], but Shailen quoting Naturale also mentions dysuria, obstructive voiding symptoms, weight loss, abdominal pain, ureteral obstruction, recurrent urinary tract infections [2,6]. These symptoms are nevertheless rather unspecific and will rarely point to this type of pathology by themselves.

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Etiology

Several theories have been proposed to explain the development of this tumors. The first theory, and so far the most widely accepted, is that SCCB originates from a multipotential stem cell. This theory could also explain why a considerable number of SCCBs coexist with other bladder malignancies, most prominently transitional cell carcinoma (TCC). Also, the field-effect theory postulates that a common carcinogen produces changes in the cells of the bladder, thus causing multicentric tumors. In this case, smoking has been shown to be associated with the development of both tumors. The second theory posits that these tumors arise from neuroendocrine cells that are normally found among the urothelial cells. Although these cells are scarce and the understanding upon them is limited, it is assumed that they are cells similar to the enterochromaffin cells in the gut, the Amine-Precursor Uptake and Decarboxylation System (APUD). This theory is supported by the article of Emad at al. concerning the involvement of serotonin and serotonin antagonists on bladder cancer proliferation in mice which shows that the neuroendocrine cells do not proliferate by themselves, but create a fertile environment that encourages tumor growth, differentiation and angiogenesis by releasing growth factors and neuropeptides (serotonin, 5-hydroxytryptamine, somatostatin, bombesin) [7]. The third and last theory suggests that NETs originate in the neuroendocrine cells within the normal or metaplastic urothelium [8].

Diagnosis

In the majority of cases, the most common presenting symptom was painless hematuria (68.2% in Choong's study) [1]. But as pointed out by the Oxford Handbook of Urology, asymptomatic hematuria can have causes that range from simple urinary tract infections, nephrological pathologies or even systemic pathologies such as arterial hypertension, and most importantly, bladder cancers [9]. Other authors, as well as Choong, mention other presenting symptoms with variable frequencies: urethral obstruction, dysuria, obstructive voiding symptoms, recurrent urinary tract infections, nocturia, frequency, abdominal pain, weight loss, paraneoplastic syndromes.

The most important part of the diagnostic algorithm is the tumor pathology. Most urologists will perform a cystoscopy which will allow them to assess the tumor size and location and thus decide if a transurethral resection of the bladder is a viable diagnostic or even therapeutic alternative. As described by Choong et al., the mean tumor size in their study was 5.1 cm [1]. According to the retrospective review in the Anglian Cancer Network, 54% occurred in the lateral walls, 20% in the posterior wall, 10% in the trigone, 8% in the dome and 8% in the anterior wall [10]. Choong also mentions one patient with a developing tumor in a bladder diverticulum and a patient with a tumor growing from the urachal remnant, but these instances remain exceptions, though they should be taken into consideration by the physicians [1].

During the cystoscopy, macroscopically the tumors are usually large, with a polypoid or nodular aspect with superficial necrosis in most cases. Macroscopically, small-cell carcinoma is not different from urothelial carcinoma and in 40% of cases they may co-exist [1].

The next step is either transurethral resection of the bladder tumor (TURBT) or bladder biopsies. The pathologist will examine the specimen according to the WHO classification of neuroendocrine tumors and elicit one of the following results regarding their grade of differentiation:

1. Well differentiated (benign or with uncertain behavior) – G1
2. Well differentiated with a low grade malignant behavior – G2
3. Poorly differentiated with a high grade malignant behavior – G3
    - Small cell carcinoma
    - Large cell carcinoma.

This result will be given after the evaluation of the mitotic count and the Ki67 index, as presented in Table I.

Table I. Grade of neuroendocrine tumors according to WHO [11].

Grade	G1	G2	G3
Ki67 index (%)	<2	3-20	>20
Mitotic count	<2	2-20	>20
Diagnosis	**Neuroendocrine tumor (carcinoid)**		**Neuroendocrine carcinoma**

The light microscopy shows sheets and nests of small round or oval cells, occasionally spindled (10-14 microns), that are loosely attached to each other, with a hyperchromatic coarsely granular chromatin, evenly dispersed with a "salt and pepper" appearance, scant cytoplasm with rare organelles and inconspicuous nucleoli, high nuclear-to-cytoplasm ratio. The electron microscopy can reveal neurosecretory granules inside these cells. The diagnosis can be made difficult in small biopsy specimens because of the Azzopardi phenomenon (crush artifact), which is due to the presence of DNA in necrotic venules. Mitoses are frequent with more than 20 mitoses/HPF (high-power field).

An important part of the pathological diagnosis is the immunohistochemical study and in this case, the small-cell carcinoma will show both epithelial and neuroendocrine differentiation. According to the Canadian Association of Genitourinary Medical Oncologists, the markers of neuroendocrine differentiation most commonly positive are neuron-specific enolase (25-100%), chromogranin A (22-89%), synaptophysin (67-76%), CD 57, Cd56 and protein gene product 9.5 [12]. Immunohistochemistry with anti-chromogranin A and anti-synpatophysin antibodies must be used for all poorly differentiated or undifferentiated tumor components in order to guide the course of treatment, and staining with neuron-specific enolase should be included in pre-treatment staging (13). Epithelial markers that can be present in small-cell carcinoma are cytokeratin 7 (60%), epithelial membrane antigen (80%), CAM5.2 and CK8/18. Cytokeratin CAM5.2 is present in both urothelial carcinoma and small-cell carcinoma, but the pattern of staining is punctate along the membrane in the first case, and perinuclear in the latter [13].

The pathological differential diagnosis should be made with large-cell carcinoma and carcinoid tumor of the bladder. Large-cell carcinoma presents with large cells of polygonal shape, low nuclear-to-cytoplasm ratio, coarse chromatin, frequent nucleoli, rosette-like structures and high mitotic activity. Markers for neuroendocrine differentiation are present in similar fashion as in the small-cell carcinoma. The carcinoid tumors present with cuboidal or columnar cells, with granular eosinophilic cytoplasm, with round-oval nuclei containing finely stippled chromatin and inconspicuous nucleoli, without necrosis or crush artifact, but with markers of neuroendocrine differentiation in immunohistochemistry studies [11].

Other differential diagnosis should be made with high-grade urothelial carcinoma, lymphoma, lymphoepithelial-like carcinoma from the lung, metastases from another neuroendocrine tumor (lung), neuroendocrine carcinoma of the prostate infiltrating the bladder, rhabdomyosarcoma (in children) [1,13].

Soriano et al. have noted molecular abnormalities in small-cell carcinoma of the bladder, including positive immunostaining for p53 (80%), c-erbB2 (50%), c-kit and EGFR (30%), thus raising the question of using therapies targeting these mutations (trastuzumab – Herceptin™, imatinib – Gleevec™, EGFR inhibitors – geftinib, erlotinib).

Cheng et al. discovered nearly identical patterns of allelic loss (loss of heterozygosity in five polymorphic microsatellite markers: DS3050, IFNA, D9S171 and TP53) in small-cell carcinoma and in concurrent urothelial carcinoma in a series of patients, but also identical X-inactivation in these cells in four women patients. These findings suggest a common origin for these tumors with a biphenotypic differentiation after carcinogenesis is initiated.

Usually, the urologist will order staging investigations to study the extent of the disease. The Canadian Association of Genitourinary Medical Oncologists recommends an abdomen and pelvis contrast-enhanced computer tomography, including CT urography to search for defects in collecting systems, MRI for extravescial extension and adjacent organ invasion (especially before radical cystectomy), 99mTC-MDP bone scans for diagnosing bone metastases, gadolinium-enhanced MRI for suspicion of brain metastases [12].

Treatment

Small-cell carcinoma of the urinary bladder is a rare pathology andthe data regarding the treatment are scarce, therefore we currently have no standard of treatment. Most of the options are extrapolated from small-cell carcinoma of the lung, especially regarding the chemotherapy options, but not regarding the surgical ones.

Treatment options include:

1. Chemotherapy alone
2. Neoadjuvant chemotherapy followed by cystectomy
3. Cystectomy followed by adjuvant chemotherapy
4. Cystectomy alone
5. Transurethral resection of the bladder alone (TURBT)
6. Radiotherapy alone
7. Concurrent or sequential chemotherapy and radiotherapy.

The National Comprehensive Cancer Network's guidelines of 2015 recommend resection and chemotherapy (as for small-cell lung carcinoma) with or without radiotherapy for non-locally advanced tumor, radiotherapy and chemotherapy for locoregional advanced disease, and chemotherapy alone for metastatic disease [16].

In the studies found in the literature, we found evidence that TURBT alone was an inadequate method of control of the disease due to its aggressive nature, even in limited disease. Lynch and colleagues discovered that in combined treatment modalities (neoadjuvant chemotherapy+cystectomy versus cystectomy+adjuvant chemotherapy), the median overall survival was 159.5

months in the first group and 18.3 months in the latter [17]. Siefker-Radtke and colleagues also present better results with neoadjuvant chemotherapy and cystectomy [18]. Both authors note that the patients who obtained downstaging to <pT2 had a better median overall survival, and Siefker-Radtke mentions that in a 2-year follow-up none of the patients had cancer-related deaths. On the other hand, Cheng et al. observed no significant difference in overall survival in patients who benefited from cystectomy versus those who did not [15].

The chemotherapy regimens used depend on the pathological findings and the extent of the disease. Mixed small-cell carcinoma responds to MVAC regimen (methotrexate, vinblastine, adriamycin, cisplatin), pure small-cell carcinoma responds to cisplatin-etoposide or etoposide or ifosfamide/doxorubicin regimen [13,19]. Carboplatin can be considered as a substitute for cisplatin in patients with major comorbidities or low performance status, due to its lower level of myelosuppresion and alsocisplatin intense nephrotoxity and neurotoxicity. In patients with extensive, metastatic disease the impact of chemotherapy on survival is minimal, thus its role is merely palliative [12]. Adjuvant platinum-based chemotherapy is shown in Choong's study to have no significant improvement in patients with stage II disease, after radical cystectomy, but may prove of use in clinical context in patients with stage III or IV [1].

Radiation doses used in combination with chemotherapy varied from 35 Gy/20, 64 Gy/32 to 70 Gy [12]. Chemotherapy regimens used in combination with radiotherapy were carboplatin-etoposide, vindesine-ifosfamide-cisplatin, cisplatin-doxorubicin-vincristine-etoposide, cyclophosphamide-methotrexate-vinblastine. Bex et al. [12,20] report that patients with limited disease receiving chemoradiation had a median overall survival of 15 months, one month more than those receiving chemotherapy alone. The Surveillance, Epidemiology and End Results (SEER) database shows that chemotherapy improved overall survival in all stages of disease, while radiotherapy improved survival in patients in limited disease [5]. London Health Sciences Center recommends assessing patients under bladder-sparing therapies after 2 cycles of chemotherapy with cystoscopy and CT scans. Evidence of disease progression should lead directly to cystectomy [21].

Conclusion

Small-cell carcinoma of the bladder is a rare type of cancer, accounting for less than 1% of bladder cancers. Clinical findings are inconclusive and patients present at a later stage than in urothelial carcinomas. The typical patient is a 60-year old Caucasian male with a history of smoking presenting with gross painless hematuria. Treatment options are not standardized, though so far it seems that neoadjuvant platinum-based chemotherapy followed by cystectomy offers the best outcome, except when metastases are present, in which case chemotherapy alone offers palliative support.

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