REVIEW

Diagnosis and treatment in primary bladder small cell carcinoma: Literature review

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Summary	*Small cell bladder carcinoma is a rare and frequently fatal disease. It can be distinguished from classical urothelial carcinoma microscopically and immunohistochemically. Small cell bladder carcinoma has histologically similar properties with other small cell carcinomas in other organs. It has a worse prognosis when compared to urothelial bladder cancer. Multimodal treatments are recommended although there is no widely accepted consensus regarding to the treatment algorithm because of its rarity. In this review, clinical properties and diagnosis of small cell bladder carcinoma, its histopathological and immunohistochemical properties and treatment modalities are examined.*

KEY WORDS: *Neuroendocrine carcinoma; Bladder cancer; Small cell cancer.*

INTRODUCTION

Neuroendocrine tumors (NET) are a heterogeneous group of tumors that developed from neuroendocrine cells. They are separated in sub categories according to the organs from which they originate. NET was first described in the bronchopulmonary tract by Barnard in 1926 (1). Small cell carcinoma (SmCC) is developed from the lower respiratory tract and spreads out rapidly and is common in chronic smokers. SmCC may develop in extrapulmonary regions and its diagnostic criteria are the same as in pulmonary SmCC. Uniform small cells with scant cytoplasm, salt-pepper like chromatin and inconspicuous nucleoli are the diagnostic findings.
Extrapulmonary NET can develop from almost every part of the body except central nervous system. Primary location can be esophagus, gastrointestinal tract, pancreatobiliary system, larynx, salivary glands, uterus, cervix uteri, vagina, bladder, prostate, breast, lacrimal gland and dermis. In urinary system, NET was firstly described by Resnick in 1966 as a carcinoid subtype in the kidney whereas 1977, Wenk described NET with SmCC subtype in the prostate. Regarding to bladder, Cramer has first described NET in 1981 with a sub-type of SmCC (1). Today in the urinary system, NET is most frequently observed in the bladder, then prostate, kidneys and ureter respectively (1). NET, both pulmonary or extrapulmonary,

develops from cells of the same origin. There are two different theories regarding to the origin of the cells. According the first theory, amine precursor uptake and decarboxylation (APUD) cells take origin from neural crest and migrate to different epithelial areas in the body. APUD cells present intracytoplasmic neurosecretory granules and can be positively stained with chromogranin A (CGA). According the second theory, clonality studies have shown that NET is originated from multipotent root cells that can be converted in different tissue types. Thus cancers have similar molecular abnormalities.

EPIDEMIOLOGY

Bladder carcinoma (BC) is the fourth most frequent cancer in men and is responsible for 14,000 cancer-related deaths in United States of America annually (2). 90% of BC is urothelial carcinoma and the most frequently types out of urothelial carcinoma are squamous cell carcinoma and adenocarcinoma (2, 3). SmCC is a rare form of BC and responsible for < 1% of primary BC (3). SmCC is frequently seen in men in seventh or eighth decade (1, 4, 5). Its incidence between 1991 and 2005 in United States of America has increased from 0.05 to 0.14 in 100.000 inhabitants (3). In men, it is observed as 3 times more than women and in white race, it is observed as 10 times more than the other-than-white races (3). It is more frequent in advanced age and average incidence age is 71 years (4-6). Smoking is considered to be a risk factor and smoking history is present in 50-70% of SmCC patients (7). In most of the patients, there are non-specific risk factors such as bladder stone, bladder manipulation and chronic cystitis (4, 5, 7). Exposure to second-hand smoking and chemicals is controversial (7).

CLINICAL PROPERTIES AND DIAGNOSIS

SmCC BC is similar to bladder urothelial carcinoma in terms of age of onset, gender and symptoms. It presents with local, systemic or paraneoplastic symptoms. The most frequent symptom is painless gross hematuria that is observed in 80-90% (1, 4, 7, 8). Dysuria, obstructive voiding symptoms, abdominal pain, pelvic pain and recurrent urinary tract infection are other frequently observed symptoms. Sometimes it may also occur with

systemic symptoms such as weight loss and fatigue. It can rarely present by a paraneoplastic syndrome although less frequently when compared to pulmonary SmCC. Paraneoplastic syndrome may cause hypercalcemia, hypophosphatemia, Cushing syndrome and sensorial neuropathy (9, 10).

SmCC and urothelial BC cannot be definitely differentiated via imaging methods. Computerized tomography (CT) of urothelial carcinoma shows in 70-80% a focal asymmetric bladder wall thickening occurs and in 20% the muscle invasive carcinoma is demonstrated as a solitary mass (11). At CT, SmCC presents as large solitary lesion consisting of necrosis and calcifications at different ratios. Frequently, diffuse bladder wall thickening is seen and extension to perivesical fat and surrounding tissues occurs (11).

Diagnosis is made by cystoscopy and microscopic evaluation of the tissue obtained via transurethral resection of bladder tumor (TUR-BT). Macroscopically it presents as a polypoid mass from 1,5 to 13 cm large (4, 11, 12). Despite most of the tumors are located on the lateral wall of the bladder, they may less often located on the base, trigon, anterior wall and fornix of the bladder (1, 4, 8). Lesional cells can be observed in the urine cytology (13). Histopathological and immunohistochemical assessment Microscopically SmCC BC is similar to SmCC in other organs and classification is performed according to the World Health Organization (WHO) classification system. Although tumor occurs as a diffuse growth without pattern, sometimes focal nests and trabecula can be seen (14). Nests are formed of small or medium-size cells. Cells are formed by round oval overlapping nuclei and regularly distributed salt-and-pepper like chromatin and inconspicuous nucleoli (14). Cytoplasm of the cells is scarce and organelles are rare. Frequently mitosis, crush artifact and geographical necrosis are seen. Azzopardi effect (crush artifact) is the indicator of high proliferation ratio. Electron microscopy shows the presence of membrane-limited dense core granules with a diameter of 150-250 mm (9).

Bladder SmCC is in mixed type more frequently when compared to pulmonary. It is 40-70% mixed and most frequently is accompanied to urothelial carcinoma (13, 15). According to their frequency, it may be accompanied also to squamous cell carcinoma, adenocarcinoma and rarely sarcomatoid carcinoma (15). Prognosis of mixed tumors, even if SmCC is present in a small focal area, is similar to the bad prognosis of pure SmCC (8, 16). Thus it should be always demonstrated whether there is presence SmCC in classical urothelial carcinoma or not.

In case of rarely seen diagnostic difficulties, immunohistochemical staining may be applied to verify the diagnosis. Thus synaptophysin, CGA, neuron specific enolase (NSE), CD56 and similar staining can be applied although their sensitivity for bladder SmCC is relatively low (15). Independent morphologic appearance of bladder SmCC should be sufficient according to WHO diagnosis criteria (13).

CGA is also known as parathyroid secretory protein 1 and coded by the CHGA gene. Because it is related to the release of amine/peptide, CGA is expressed from β cells of pancreas in the cells similar to enterochromaffin and in chromaffin cells although it is not present in steroid hormone producing cells (13). It is the neuroendocrine marker for bladder SmCC with the lowest sensitivity and it is stained with a one-third to one-half ratio (15). A 5% positivity is observed in urothelial bladder carcinoma (17). Synaptophysin is known as the major synaptic vesicle protein p38 and coded by the SYP gene. It is present in all the cells producing amine/peptide and steroid hormone and in all the neurons (13). CD56 is known as the neural cell adhesion molecule and coded by the NCAM1 gene. It is present in the membrane of neurons, glia, skeletal muscles and natural killer cells (13). For bladder SmCC, the sensitivity of synaptophysin and CD56 is higher than CGA. In a study of *Buza et al.*, they have found sensitivity of CD56 as 71.4% and suggested that it is the most sensitive marker for the bladder SmCC (18). In the same study, sensitivities of synaptophysin and CGA are found as 64.3% and 28.6% respectively (18).

NSE is known as γ-enolase or enolase 2 and coded by the ENO2 gene. It shows phosphopyruvate hydratase activity and is present in mature neuron cells. Its sensitivity for bladder SmCC is about 80% and its specificity is very low (14, 18, 19).

Thyroid transcription factor 1 (TTF-1) is known as NK2 homeobox 1 and coded by the NKX2-1 gene. It is the transcription factor that is produced in thyroid follicular cells, Clara cells and type 2 pneumocytes in the lungs and diencephalon in the brain (13). *Cheuk et al.* have found the sensitivity of TTF-1 for extrapulmonary SmCC as 42% (20). *Jones et al.* have observed TTF-1 positivity in the bladder SmCC in 50% (21). No relationship between TTF-1 expression and the prognosis of bladder SmCC is found (21). Thus it is not reliable for the diagnosis of primary SmCC and there is no prognosis anticipation.

The p53 is coded by the TP53 gene and it is a tumor suppressor protein. Various cancers are developed by the mutation of p53 and these generally progress by poor prognosis. A p53 overexpression in bladder SmCC is seen between 37 and 80% (13, 14). No relationship between p53 overexpression and the prognosis of bladder SmCC is found (14).

The p16 is known as cycline-dependent kinase inhibitor 2A and coded by the CDKN2A gene (13). It takes place in the regulation of p16 cell cycle and various cancers develop by the p16-retinoblastoma pathway in its mutations. Normal tissues and normal urothelial mucosa has heterogeneous staining pattern with p16 and is positive in 1-10% (22). In the study of *Buza et al.* in which they have taken 10% as the limit value for abnormal p16 staining, they have found p16 positivity as 92.8 in bladder SmCC and as 43.7 in high-grade urothelial carcinoma (18). This data shows that the changes in p16-retinoblastoma pathway are required for the development of bladder SmCC.

The p63 is known as the transformation-related protein 63 and coded by the TP63 gene (13). It is a member of p53 family and it features as a transcription factor. The p63 activity is different between the bladder SmCC and high-grade urothelial carcinoma. While p63 is found negative in 92.8% of the patients with bladder SmCC, it

is found positive in 81.3% of the patients with urothelial carcinoma (18). Thus p63 is an immunohistochemical marker that may help to differentiate the bladder SmCC and urothelial carcinoma.

Various cytokeratin stains were also studied in bladder tumors. CK20 expression shows that tumor aggressiveness is low. While *Buza et al.* found the CK7 positivity as 64.3% in the bladder SmCC, CK20 was only stained focally in 2 cases (18). In bladder SmCC, CAM 5.2 is found positive in 60-70%, 34βE12 in 40-45% and epithelial membrane antigen as 75-80% (4, 5, 13-15, 17, 18, 20, 21).

Uroplakin is a urothelium-specific transmembrane protein and it is a terminal urothelial cytodifferentiation marker. Despite it is positive at various ratios in the bladder urothelial carcinoma, *Jones et al.* have found it negative in all 44 patients with SmCC (21). There are also studies regarding to the c-kit that is a transmembrane tyrosine kinase receptor and proto-oncogene (CD117) and also human epidermal growth factor receptor 2 (Her2/neu) with positivity between 30 and 50% is found (10). Positivity of these two markers may be important in terms of treatment and prognosis in the future.

In the diagnosis of bladder SmCC, the differentiation between poor differentiated urothelial carcinoma, alveolar rhabdomyosarcoma, lymphoma, lung SmCC metastasis and spreading of SmCC of adjacent organs should be done. Immunohistochemical studies help for the differential diagnosis instead of diagnosis. In prostatic SmCC, prostate-specific antigen is frequently negative and it does not assist in the differentiation of bladder SmCC. In prostatic SmCC, p501s and prostate membrane antigen is low (approximately 20%) positive. Although the determination of TMPRSS2-ERG gene fusion establishes the diagnosis of prostatic SmCC, it does not exclude the prostatic origin (13). Alveolar rhabdomyosarcomas may not show the classical alveolar structure and they help positive staining by myogenin, MyoD1 and desmine that show muscle differentiation (10, 13). Non-Hodgkin lymphoma is differentiated from bladder SmCC because of positive CD45 and negative CK (10).

STAGING AND TREATMENT

In simple staging used for lung SmCC, the disease is divided in *"limited"* and *"extensive"* (10). Limited disease consists of a single radiotherapy port or operation area. In 2007, International Association for the Study of Lung Cancer group has recommended tumor-node-metastasis (TNM) staging for lung SmCC because it is well related to the prognosis of the patients (10). According to our own experiences, TNM staging for bladder SmCC is better in the suggestion of prognosis. As in the bladder tumors, thorax and abdomen CT are standard approaches for staging. Because magnetic resonance imaging shows the distribution of local disease better than CT, *Moretto et al.* recommend it in the patients for whom radical cystectomy is planned (10). Due to the risk of lymph nodes, liver and bone metastasis and less often of lung and brain metastasis of the disease, some clinicians also recommend 99mTc-MDP bone scanning and 18F-FDG positron emission tomography (9, 10). CT-urography for

demonstration of filling defect in the urinary tract is controversial (10, 11).

Multimodal approach is suggested in the treatment (9, 10). Because it is a rarely-seen disease, there is no treatment scheme (guideline) except that of the *Canadian Association of Genitourinary Medical Oncologists* (9, 10), but they refers to the results of a single center retrospective study and their evidence and suggestion levels are low. While surgery, surgery and adjuvant or neoadjuvant chemotherapy and surgery and/or chemotherapy can be applied for the limited disease, only chemotherapy can be applied in extensive diseases.

Individual surgery options are radical cystectomy and TUR-BT. Simple TUR-BT treatment is an insufficient option for the disease control due to high recurrence ratio and a survival period of 3-6 months (9, 23). However, if the general status of the patient does not permit any other treatment modality, it can be applied in this limited patient group. *Cheng et al.* cannot find 5-year survival difference between the patients with and without individual radial cystectomy (%15 vs. %18, p = 0,65) (4) although *Choong et al.* have shown a 5-year survival in the patients to whom individual radical cystectomy was applied of 63.6% (12). These studies have shown that surgery alone, even if radical cystectomy is applied, does not extend survival in the patients except in selected ones. The combination of surgery and neoadjuvant chemotherapy increases long-term survival ratios. In fact bladder SmCC is a systemic disease, even if not initially demonstrated, and its cells respond to platinum-based chemotherapies. The more frequently used chemotherapy protocol is a 3-week cycle including intravenous etoposide 100 mg/m^2 dose on 1st-3rd day and intravenous cisplatin 70-100 mg/m^2 on the 1st day (24, 25). Carboplatin may be changed with cisplatin due to its better toxicity profile. It is argued that the disease is down-staged by preoperative chemotherapy and that chemosensitive micro metastases are treated and accordingly the survival periods could be increased. When *Siefker-Radtke et al.* have compared patients treated with radical cystectomy after preoperative chemotherapy to those treated with radical cystectomy alone, they found that the 5-year survival period was 78% and 36% respectively (26). *Siefker-Radtke et al.* have determined in another study that pathologic downstaging was present in 78% of the patients via neoadjuvant chemotherapy and median overall survival was 58 months (24). The results of Lynch et al. about neoadjuvant chemotherapy are more dramatic. In their study, radical cystectomy after neoadjuvant chemotherapy and radical cystectomy alone and adjuvant chemotherapy after radical cystectomy were compared. In the patients to whom radical cystectomy had been applied after neoadjuvant chemotherapy, median survival was found as 159.5 months and 5-year survival was found as 79% (25). The results of the other arms of the study were similar to the literature. In short, neoadjuvant chemotherapy and radical cystectomy in the patients who are suitable for surgery seems to be the gold standard treatment.

Application of radiotherapy and surgery and/or chemotherapy is a bladder-protective method and can be an alternative to cystectomy. Chemoradiotherapy can be

applied simultaneously or successively. *Lohrisch et al.* reported a 44% 5-year survival in 10 patients after chemoradiotherapy (9). Bex et al. obtained a complete response in 88% of 17 patients via chemoradiotherapy after TURBT and median overall survival was found as 32.5 months. The 5-year survival was calculated as 36% (27). Trimodal approach can be applied as an alternative method in the patients who are not suitable for operation or who do not want radical cystectomy and especially in the patients with low performance status.

At the time of diagnosis, prognosis of metastatic SmCC is poor and median survival is between 5 and 13 months (8, 16, 27). Platin-based chemotherapy regime is the standard treatment (8, 12, 16, 26). As an alternative regime, iphosphamide-doxorubicin can be used and as single agent, also paclitaxel and irinotecan can be used (8, 12, 26). Despite it is chemosensive, overall survival is relatively poor. When the disease relapse is observed after the treatment, the same induction regime can be applied by considering the response to the first treatment and the disease-free interval. Otherwise second-line chemotherapy regimes can be used and, as a single agent, topetecan or vinorelbine can be used (28). As a combination, CAV (cyclophosphamide, doxorubicin, vincristine) regime can be used (28). Response ratios to the second-line regimes are variable. Radiotherapy can be used as palliative in the patients who have symptomatic bone metastasis or brain metastasis.

Although there are some clinicians recommending prophylactic cranial radiotherapy due to the combination of advanced stage disease and brain metastasis, there is no exact data regarding to its efficiency (9). Prognosis of the patient is related to his performance status and the spreading of the disease at the time of diagnosis. No relation is found between the age, gender, symptoms of the patient and p53 and prognosis (8, 9, 13). Histologically the patients with pure SmCC can have poorer prognosis than the patients with mixed SmCC (16).

CONCLUSION

Bladder small cell carcinoma is biologically an aggressive tumor and it is in most of cases in the advanced or metastatic stage at the time of diagnosis. Diagnosis can be easily made by microscopic examination.

Immunohistochemical stainings are supportive for diagnosis. Its prognosis is poor and multimodal approach is recommended in the treatment. It is important to refer the patients to centers with experience of multimodal treatment. In limited disease, radical cystectomy after platinum-based adjuvant chemotherapy seems to be the best treatment method.

In extensive diseases, chemotherapy is the primary treatment. Studies explaining the molecular pathogenesis are needed and will be instructive for the diagnosis and treatment of the disease.

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