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Small cell carcinoma of the urinary bladder – literature review

Elżbieta Czykier*,

Department of Histology and Embryology, Medical University of Bialystok, Waszyngtona 13, 15-269 Bialystok

Barbara Darewicz

Department of Urology, Medical University of Bialystok, M. Sklodowskiej-Curie 24a, 15-276 Bialystok

Mateusz Puchalski

Students „Interdisciplinary" Scientific Group at the Department of Histology and Embryology, Medical University of Bialystok, Waszyngtona 13, 15-269 Bialystok

*Corresponding author: Elżbieta Czykier, Department of Histology and Embryology, Medical University of Bialystok, Waszyngtona 13, 15-269 Bialystok, tel/fax (+48 85) 748 54 55, e-mail: czykier@umb.edu.pl

Abstract: Neuroendocrine neoplasms (NENs) are epithelial neoplasm with prominent neuroendocrine differentiation. NENs are frequent in the respiratory and gastrointestinal tract, but they can arise in any organ. Extra-pulmonary localization of NENs are the larynx, salivary glands, the uterus, the cervix uteri, the vagina, the prostate and the urinary bladder. Small cell carcinoma of the urinary bladder (SCCB) is a type of neuroendocrine neoplasm. In order to be included in the review, articles from PubMed (NCBI), Google Scholar, Web of Science and Scopus archive had to fit the following criteria:
- They had to be original articles, case studies and reviews connected with the following key words: neuroendocrine neoplasms, small cell carcinoma, urinary bladder, epidemiology, pathogenesis, diagnosis, histopathology, treatment and prognosis.
- They had to be written in English.
- They had to be published between 1981 and 2018, as the first article about small cell carcinoma of the urinary bladder was written by Cramer et al. in 1981.
SCCB is an extremely rare tumor, however it is highly malignant and is characterized by very aggressive behavior. The origin of the disease is unknown; the majority of patients are male in their sixties and seventies with a history of smoking tobacco products. Clinical symptoms of SCCB are not characteristic and include severe pain and hematuria. During cystoscopy macroscopically it is visible as a polypoid tumor. The image in a microscopic sample is dominated by small, round tumor cells infiltrating the urinary bladder wall. Immunoreactivity of these cells is very low for conventional neuroendocrine markers such as synaptophysin, chromogranin A and CD56. Since SCCB is so rare, no universal standard treatment has yet to be developed. Treatment includes chemotherapy, radiotherapy as well as surgical procedures. The prognosis of SCCB is very poor and the tumor tends to spread to the bones, the brain and the liver. Average survival rates of patients diagnosed with SCCB range from 12 to 24 months.

1. Introduction

Neuroendocrine neoplasms (NENs) are epithelial tumors with prominent neuroendocrine differentiation. NENs can arise from any type of epithelium, but frequently develop from epithelia rich in enterochromafin cells. These cells are numerous in the gastrointestinal tract, and also appear in the respiratory tract, which develops from the primary gastrointestinal bud. Small amounts of enterochromafin cells are also found in the genitourinary system as well, particularly in the urinary bladder and prostate (Ghervan, Zaharie et al. 2017). Neuroendocrine neoplasms belong to a very rare neoplasm in the human body. They occur at a rate of 2.5 to 5 incidences per 100,000 people per year (Oberg, Castellano 2011). Current research shows that there are year on year increases in the incidence of NENs, both in the United States and in other countries (Dasari, Shen et al. 2017, Hauso, Gustafson et al 2008, Hallet, Law et al. 2015).

NENs most often develop in the respiratory and gastrointestinal tracts but can arise in any organ. Extra-pulmonary localization of NENs are the larynx, salivary glands, the uterus, the cervix uteri, the vagina, the prostate and the urinary bladder (Zhao, Flynn 2012). Neuroendocrine neoplasms are a heterogenous group of tumors very different in clinical behavior depending on where they appear. In 2017, experts of the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) finally classified them as neuroendocrine neoplasms and decided that "the key feature of the new classification is a distinction between differentiated neuroendocrine tumors (NETs) also designated carcinoid tumors in some systems, and poorly differentiated neuroendocrine carcinoma (NECs), as they both share common expression of neuroendocrine markers". At the time of discussion of the new classifica-

tion, experts took into account six major points: anatomy, tumor category definition, tumor family definition, tumor-type definition, tumor sub-type definition, and tumor grading procedures. According to the above classification regarding the genitourinary system, experts distinguished between well-differentiated NENs - neuroendocrine tumors (NETs) G1, G2, G3, as well as poorly differentiated NENs – neuroendocrine carcinoma (NECs) G3 as small cell type, and large cell type (Rindi, Klimstra et al. 2018).

Small cell carcinoma (SCC) belongs to a very rarely occurring type of neoplasm and develops in various systems and organs, including the gastrointestinal tract, pancreatobiliary system, larynx, salivary glands, uterus, cervix uteri, vagina, prostate and urinary bladder (Davis, Ludwig et al. 1983, Kim, Lin et al. 1984, Dores, Qubaiah et al. 2015).

The most frequently occurring location of SCC is in the lungs, which account for 15% of all bronchogenic carcinoma cases (Zheng, Ettinger et al. 2013, Zheng, Liu et al. 2015). Extrapulmonary small cell carcinomas make up only about 4% of all small cell carcinomas (Jemal, Bray et al. 2008). Despite its appearance in different organs, SCC is characterized by a similar histological structure, whereas its clinical behavior is very different depending on its location.

Small cell carcinoma of the urinary bladder (SCCB) is a type of small cell carcinoma. The goal of this work is to review the literature concerning the extremely rare occurrence of small cell carcinoma of the urinary bladder.

2. Search strategy and selection criteria

The goal of this work is to collate up-to-date knowledge on the subject of the etiology, pathogenesis, clinical symptoms, diagnosis, treatment and prognosis of the course of small cell carcinoma of the urinary bladder. To carry out the study, the following databases were used: PubMed (NCBI), Google Scholar, Web of Science and Scopus, using the following key words: neuroendocrine neoplasms, small cell carcinoma, urinary bladder, epidemiology, pathogenesis, diagnosis, histopathology, treatment and prognosis. We searched through original articles, case studies, and reviews published between 1981 to 2018. The results of the study includes alternative keywords submitted to put together a complete picture of this cancerous condition.

3. Epidemiology

Small cell carcinoma of the bladder is a very rare disease, occurring in 0.3 to 0.7% of all primary tumors in this organ, and is characterized by very aggressive and quick growth, as well as negative prognosis. (Blomjous, Vos et al. 1989, Holmang, Borghede et al 1995, Mackey, Au et al. 1998). The first case of SCCB was described in 1981 by Cramer, Aikawa et al. Patients with SCCB were mostly men, with an overall ratio of men to women being 5:1, with a range from 1:1 to 16:1 (Quek, Nichols et al. 2005, Bex, Nieuwenhuijzen et al. 2005, Mukesh, Cook et al. 2009, Mangar, Logue et al. 2004). Most SCCB patients are over 60 years old (Dores, Qubaiah et al. 2015). The average age of patients diagnosed for the first time with SCCB is 66.9 years old with a range from 32 to 91 years of age (Choong, Queveda et al. 2005, Cheng, Pan et al. 2004, Iczkowski, Shanks et al. 1999, Siefker-Radtke, Dinney et al. 2004). Similar to patients suffering from transitional cell carcinoma, SCCB patients are smokers (from 65% to 79%) (Chen, Liu et al. 2017, Lohrish, Murray et al. 1999, Ismaili, Elkarak et al. 2008). It is therefore assumed that smoking may be one of SCCB's etiological factors. Smoking may cause similar genetic lesions in the urinary bladder (Abbosh, Wang et al. 2008). Other environmental and individual risk factors are not mentioned in the etiology of this neoplasm, but can include chronic cystitis, bladder stones, bladder manipulation or cytoplasty (Anthony, Douglas 2013, Church, Bahl 2006)). The majority of SCCB patients are white men, making up 74-97% of all cases (Choong, Queveda et al. 2005, Abrahams, Moran et al. 2005, Siefker-Radtke, Dinney et al. 2004).

4. Pathogenesis

The pathogenesis of SCCB still remains unknown. It is presumed that small cell carcinoma of the urinary bladder can be associated with chromosomal aberrations, such as hypermethylation of tumor-suppressor gene CpG islands (Abbosh, Wang et al. 2008). Similarly the origins of neuroendocrine cell carcinoma have not yet been clarified. Several theories exist that attempt to explain the origin of neuroendocrine cell carcinoma. The first theory states that malignant transformation of neuroendocrine cells leads to the development of small cell carcinoma of the urinary bladder. (Ali, Reuter et al. 1997, Trias, Algaba et al. 2001). The second theory posits that metaplastic changes of transitional epithelium lead to the progression of SCCB (Iczkowski, Shanks et al. 1999, Oesterling, Brendler et al. 1990). The third theory proposes that multipotential common stem cells affect

a specific transformation in a progression-related gene that can differentiate itself in various types of cells, including small cell carcinoma, but also in transitional cell carcinoma. (Terracciano, Richter et al. 1999, Christopher, Sefteil et al. 1991, van Hoeven, Artymyshyn 1996). The last of these theories attempts to clarify the relatively frequent coexistence of small cell carcinoma and transitional cell carcinoma of the bladder as well as the diversity of the immunohistochemical reaction encompassing both neuroendocrine markers as well as cytokeratin (Terracciano, Richter et al. 1999, Christopher, Sefteil et al. 1991, Abenoza, Manivel et al.1986, Hailemariam, Gaspert et al. 1998).

5. Clinical features

The clinical symptoms during the course of SCCB are not typical and are often displayed at an advanced stage of the neoplasm's progression. The primary symptom of SCCB is hematuria, which occurs at a frequency of 63% to 88%. (Cheng, Pan et al. 2004, Chen, Liu et al. 2017). In addition, patients complain of dysuria. (Blomjous, Vos et al. 1989, Abrahams, Moran et al. 2005). Less frequent symptoms are urinary obstruction, abdominal pain, urinary tract infection, and weight loss (Lohrish, Murray et al. 1999, Choong, Queveda et al. 2005, Abrahams, Moran et al. 2005). Occasionally, in the course of small cell carcinoma of the urinary bladder, there occur paraneoplastic syndromes characterized by hypercalcemia, hyperphosphatemia and ACTH secretion (Choong, Queveda et al. 2005, Reyes, Soneru 1985). SCCB develops insidiously and is typically discovered at an advanced stage. It also causes early metastasis in the liver, brain and bones (Saeed, Cramer et al. 2018). The average life expectancy for patients with SCCB is 12 to 24 months. (Chen, Liu et al. 2017).

6. Histopathology

Small cell carcinoma of the bladder usually forms a large polypoid or nodular tumor with extensive bladder infiltration (Zhang, Niu et al. 2017). The tumor is most often characterized by diffuse growth and sometimes develops by forming nests and trabeculae (Zhao, Flynn 2012). In the majority of cases, there is visible necrosis on the surface of the neoplasm. Macroscopically, small cell carcinoma of the bladder is indistinguishable from urothelial carcinoma of the bladder. (Cheng, Jones et al. 2005, Mukesh, Cook et al 2009). Microscopically, the structure of a small cell carcinoma of the bladder is identical to small carcinomas of other organs, i.e. the lungs or the prostate (Zhao, Flynn 2012). Tumor cells are small round or oval cells, sometimes spindled (Moretto, Wood et al. 2013, Manunta, Vicendeau et al. 2005, Soriano, Navarro et al. 2004, Yoshida, Ishida et al. 2014, Podesta, True 1989). These cells are loosely attached to one another, sometimes forming sheets or nests. The cancer cells have sparse cytoplasm with few organelles and pyknotic round or oval nuclei crowding and molding (Ismaili 2011, Zhao, Flynn 2012). The nuclei contain a hyperchromatic coarsely granular chromatin. Sometimes nuclei of these cells have chromatin that look like "salt and pepper," with a dusty appearance, inconspicuous nucleoli, and a high nuclear-to-cytoplasm ratio. In the tumor cells high mitotic activity, apoptosis, necrosis, and crush artifact (sharing of cells) is frequently observed. (Ismaili 2011). An electron microscope can show neurosecretory granules inside these cells (Kim, Lin et al. 1984).

Compared to small cell carcinoma of the lungs, approximately half of small cell carcinomas of the urinary bladder have a mixed component. The mixed epithelial component, in the majority of cases, is established as a type of urothelial carcinoma. (Ismaili, Heudel et al. 2009, Siddqui, Shabbir et al. 2006, Grignon, Ro et al. 1992).

Cancer cells exhibit expressed neuroendocrine markers such as synaptophysin, chromogranin A, and CD56, but the sensitivity of these markers is relatively low in SCCB. The least sensitive, but the most specific, of SCCB's neuroendocrine markers is chromogranin A, also referred to as *parathyroid secretory protein 1*. CD56 in turn, is referred to as the *neural cell adhesion molecule*, and is the least specific, but the most sensitive. Synaptophysin, the *major synaptic vesicle protein p38*, is of average specificity and sensitivity in relation to SCCB in comparison to chromogranin A and CD56 (Vakar-Lopez, True 2007, Yoshida, Ishida et al. 2014, Zhang, Niu et al. 2017, Moretto, Wood et al. 2013). In the diagnosis of the immunohistochemical practice, there is also a thyroid transcription factor 1 (TTF-1), the expression of which shows that this marker can also be expressed in SCCs arising in places other than the lungs.

Differential diagnosis of urinary bladder small cell carcinoma must also take into consideration large cell carcinoma and carcinoid tumors of the bladder. Neuroendocrine large cell carcinoma is characterized by large cells of a polygonal shape, a low nuclear/cytoplasmic ratio, coarse chromatin, frequent nucleoli and high mitotic activity. Neuroendocrine markers for large cell carcinoma are similar to those applied in the diagnosis of small cell carcinoma (Ghervan, Zaharie et al. 2016, Serrano, Sanchez-Mora et al. 2007, Coelho, Pe-

reira et al. 2014). Carcinoid tumors present with columnar or cuboidal cells with granular eosinophilic cytoplasm, with round or oval nuclei containing finely stippled chromatin and inconspicuous nucleoli without necrosis (Klimstra, Modlin et al. 2010). Differential diagnosis must also take into consideration small cell carcinoma of the prostate, which may have infiltrated the bladder, urothelial carcinoma, metastases from neuroendocrine tumors from the lung, as well as lymphoma, and lymphoepithelial-like carcinoma from the lung (Klimstra, Modlin et al. 2010). Recommended diagnostic procedures include an abdomen and pelvis contrast-enhanced computer tomography, an MRI to ascertain whether there has been infiltration to adjacent organs, 99mTC-MDP bone scan to make sure the cancer did not spread to the bones as well as gadolinium-enhanced MRI to check for possible spreading into the brain (Zhang, Niu et al. 2017).

7. Treatment

Small cell carcinoma of the urinary bladder belongs to a rarely occurring type of neoplasm and for this reason, there has yet to be a uniform standard of established treatment for this type of condition (Ismaili 2011). Standard practice for the treatment of this tumor includes chemotherapy, radiotherapy and invasive surgery. (Vakar-Lopez, True 2007). Chemotherapy is the standard treatment for small cell carcinoma of the lung, where in it is often applied single-handedly. The application of neoadjuvant chemotherapy is also sometimes combined with cystectomy, where cystectomy follows the course of chemotherapy, or the opposite happens, where cystectomy is the first procedure, followed by neoadjuvant chemotherapy. Cystectomy is also sometimes applied alone without chemotherapy. In certain patients, only a transurethral resection of the bladder (TURBT) is performed. There is also a method of treatment restricted solely to radiotherapy. In addition to a treatment where both chemotherapy and radiotherapy are simultaneously applied, a procedure is followed by an additional course of chemotherapy, followed again by radiotherapy.

8. Conclusion

Aggressive, quickly advancing SCCB displays distinctive clinical symptoms that give rise to neoplasms. Diagnosis of the illness usually occurs at an advanced stage, which significantly worsens the prognosis and makes effective treatment difficult. Difficulties also arise in histopathological diagnostics, since markers suitable in SCCB may have variable expression. At the same time, the very rare occurrence of these neoplasms has not yet led to the development of a uniform standard in the treatment of SCCB and therefore chemotherapy, cystectomy and radiotherapy are used in various combinations, or alone.

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