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Neuroendocrine urinary bladder tumor – as a contribution to the extending of knowledge on the urothelium

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ABSTRACT

Introduction: The structure of bladder epithelium is a very complex. Apart of main structural cells of the epithelium, there are scattered neuro-endocraine cells that form a specific system, which was called the diffuse neuroendocrine system (DNS). Facts about the DNS of the bladder epithelium is still blowing. Diffuse neuroendocrine system cell cells can undergo cancerous transformation and form a very heterogeneous group of cancers referred to neuroendocrine cancers. Urinary neuroendocrine tumors are very especially rare and location them in the urinary bladder belongs to exceptional rarity. Only a few cases can be found in world literature, therefore we decided to present our case to extend global knowledge.

Matherials and methods: To Department of Urology 109 Military Hospital was admitted 49-year-old male with gross haematuria. The ultrasound examination revealed a presence of tumor on the left wall of the bladder urinary. The preliminary diagnostic was enhanced – by CT scan. It confirmed the bladder urinary tumor without an evidence of distant metastasis. The histopathologic examination showed a pattern of high grade neuroendocrine carcinoma in at least pT2 stage. The patient was referred for radical cystectomy. During an operation a large abscess of the left kidney was disclosed. The operation was extended to left nephrectomy. The postoperative time went smoothly. Primary neuroendocraine tumors of the urinary bladder are an exceptional entity with only about 30 cases reported in the literature. Due to its rarity, additional studies are necessary to better define the optimal therapeutic management. We decided to further monitor our patient and in the case of new circumstances to present him in subsequent reports. A review of literature and treatment strategies are discussed.

Keywords: urothelium; neuroendocrine tumor; epidemiology; diagnosis; treatment.

INTRODUCTION

The structure of the bladder urinary wall is composed from 3 layers. When viewed under a microscope, the smooth muscle (detrusor) of the bladder wall is protected by outer adventitia and by inner by a mucosa. The mucosa itself consists of a tight transitional epithelium (urothelium), basement membrane and sub-urothelium. The urothelium is made up of 3 layers: a basal cell layer attached to a basement membrane, an intermediate layer and a superficial or apical layer composed of large hexagonal cells known as the "umbrella cells". An essential function of the urothelium is to offer an effective barrier between urine and underlying tissues, achieved by tight junctions between umbrella cells, severely limiting solute and water movement across the barier [1, 2]. One of often carcinomas of the bladder urinary are arising from urethelioum. But the urothelium can be also a source of extremly rare of bladder urinary tumor, which is called the neuroendocraine tumor. Neuroendocrine tumors (NETs) belong to a heterogeneous group of neoplasms which challenging both histologic examinations and medical nomenclature to match. These tumors create a large heterogeneous group derived both from the diffuse neuroendocrine system (DNS) or stem cells dispersed in the walls of the urological structures. They occur mainly in middle and old-age patients. Mostly they are asymptomatic, but they can also cause a number of non-specific symptoms such as hematuria or uropathy. The diagnosis can be established during cystoscopy and based on histopathologic examination. The term "neuroendocrine" is applied to widely dispersed cells with "neuro" and "endocrine" properties [3]. Neuroendocrine tumors account for about 0.5% of all newly diagnosed malignancies. The incidence, which is on the rise, possibly due to improved awareness, is approx. 5.86/100.000 per year with a female preponderance of around 2.5:1 [4]. In the genitourinry tract these tumors are divided in 2 groups: the first, in low and intermediate grade, described as well differantiated neuroendocraine tumors (WDNETs) and the second group to high grade tumors. The group of tumors with high grade can be distinguished also in 2 types: smal cells neuroendocraine carinoma (SCNETC) and large cells neuroendocraine carcinoma (LCNETC). Up to now, the literature were described about 25 cases of WDNETs tumors, about 30 LCNEC cases, 30 cases of LCNEC; SCNETs tumors are slightly more frequent, about 500 cases per year [5, 6].

The cell of origin of these tumors remains uncertain. Neuroendocrine cells found in the basement membrane of normal urothelium and reactive urothelial lesions may give rise to WDNET, while less differentiated NETs seem to arise from divergent differentiation of urothelial carcinoma [7]. These tumors are thought to arise from divergent differentiation of multipotent stem cells in the urothelial lining [8].

Neuroendocrine tumors of urothelial carcinoma gives worse prognosis, with more early distant metastasis other urothelial carcinoma [9].

MATHERIALS AND METHODS

An 49-year-old male was referred to Urological Department because of intensive gross hematurie with the bladder haematoma. The patient suffered from myelomeningocele. In the past he underwent bilateral amputation of his legs because of chronic infection and ankylosis but he rehabilitated very well, moving in a wheelchair with the help of the upper limbs. The first diagnostic examination was CT of the abdominis and pelvis. By contrast-enhanced CT scan was detected tumor of the bladder urinary (Fig. 1). Kidneys image was in normal shape and function. The other abdominal organs, lymph nodes were in normal shape and no evidence of metastases observed. The patient underwent transurethral resection of tumor. Intraoperatively was revealed a large tumor on the left wall, situated close to orifice of the left ureter (Fig. 2). The histopathological outcome revealed the carcinoma cells, which infiltrated the muscular layer of the urinary bladder's wall, what was an evidence for at least pT2 stage of the tumor. The carcinoma cells were immunohistochemical positively stained for chromogranin A, synaptophysin, CD56, and Ki67, panCK. This confirmed the diagnosis of a neuroendocrine carcinoma of the urinary bladder. Other markers like GATA3, PSA, AMACR, LCA and KerAE1/AES were negatively stained. The Ki67 index of the tumor was >90%. Patient was qualified to cystectomy with derivation of urine according to Bricker's procedure. Unfortunately, intraoperatively the stage of tumor was much advanced so was qualified as cT4. Thus was decided to perform total cystectomy with ureterocutaneostomy (Fig. 3). Postoperative period was smoothed and 7 days after the patient was dischared from hospital.

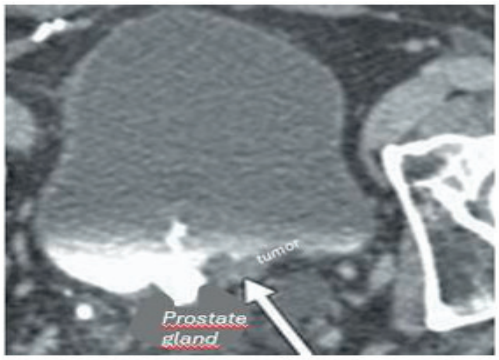

FIGURE 1. Computed tomography scan of bladder tumor. Can be notice a very close tumor location in relation to the prostate gland

The histopathologic examination was conducted in Pathomorphological Department of 109 Military Hospital. The outcome of histopathological examination of removed structures: Lymph nodes – number of lymph nodes 8 – no evidence for metastasis. Urinary bladder – high grade neuroendocrine cancer with deepness of infiltration: bladder wall, fat close to urinary bladder (periurinary fat), prostate gland. The mass of tumor was reaching the radial border of the bladder wall. Angioinvasia was present. The distal part of urethra without neoplasmatic infiltration. The other parts of the bladder wall are free from malignancies. The histopathologic staging – pT3b, N0, M0. Immunohistochemistry was performed in study no. 14162-14166/23: PANC (+), CD56 (+), Chromrogranin (+), Synaptophysin (+/–), Ki67 >90%, Gata3 (–), PSA (–) Amacr (–), LCA (–), KerAE1/AES (–).

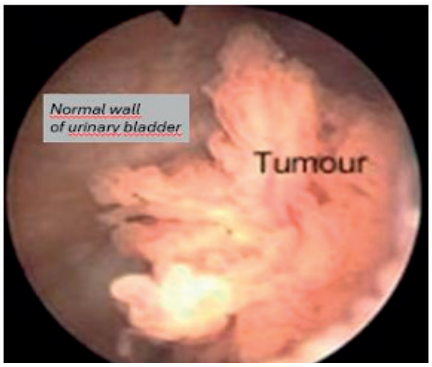

FIGURE 2. Endoscopic view during the bladder urinary tract resection procedure. Can be noticed the normal shape of urinary bladder wall with the exophytic tumor

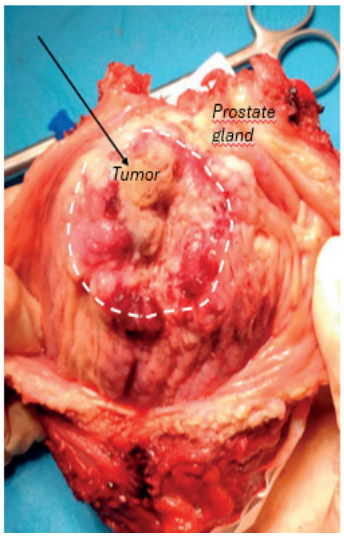

FIGURE 3. Picture of the removed urinary bladder with the tumor (black arrow)

According to the histopathological examination, the Oncological Council recommended the complementary chemotherapy. Six-months post-operative follow up showed no recurrence.

DISCUSSION

The described case of the neuroendocrine bladder tumor has increased the number of these unique urothelium tumors. The case described is also a great contribution to further research on urothelium. The neuroendocrine tumor treatment strategy is multifactorial and includes surgery, chemotherapy and radiotherapy [3, 8]. In addition to the histopathological result, the uniqueness of the described clinical case is also in encountering unusual complications. In technical aspect, nephrectomy made the most difficult surgical problems. This resulted primarily from an intensive of inflammatory infiltration including

a descending colon, duodenum and pancreas. Due to the significant of local advanced of the bladder tumor and its high malignance, the patient was withdrawn from the orthotopic urinary bladder or even from the ureterointestinal anastomosis according to the Brickker's procedure. The neuroendocrine neoplasms of urinary bladder are the extremely aggressive forms of tumors, where cure level is much below 50% [10]. The range of procedures to be used in the treatment of neuroendocrine tumor is wide and includes surgery, immunotherapy, chemotherapy or radiotherapy in various combinations [11]. This proves that there is no elaborated standard scheme of conduct with this tumor. Probabile this is a consequence of its extreme rarity. According to epidemiologic data they account about 0.5–1.0% of all bladder cancers [12]. The neuroendocraine cancers are characterized by greater aggressiveness and a worse prognosis compared to urothelial tumors. Most often at the moment of diagnosis are already in significant progress of the disease [3, 13]. Based on the presented clinical case, can be reached another conclusion that the urinary bladder epithelium hides more secrets yet, which requires further research [14].

CONCLUSION

Primary NETs of the urinary tract are much rarer than in the other organs like the lung or the gastrointestinal tract. This warrants diligent search for primaries outside the urinary tract before rendering such diagnoses. The strict collaboration between the pathologist and the urologist is essential. Despite the advances in imaging techniques, serum marker studies, and molecular diagnostics, the diagnosis of these tumors continues to be challenging. Due to the rarity of these cases, no treatment guidelines are available, and patients are usually managed using regimens extrapolated from NETs at other sites.

And therefore further reports are needed to increase the group, what will allow to better define optimal management strategies.

The bladder epithelium is a very complex and not fully known histological structure. That is why there is a constant need to deepen knowledge about its construction. The presented clinical cases can be an excellent inspiration for further researches on the urothelium.

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