

CASE REPORT

Small cell carcinoma of the urinary bladder – a new case report

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Abstract

Primary pure small cell carcinoma of the urinary bladder is an extremely rare and highly aggressive tumor with an average five-year survival rate of less than 10% as cited by multiple case reports. It accounts for about 0.5–1% of all bladder tumors. We present the case of a 44-years-old man, smoker (10 cigarettes/day) hospitalized in the Department of Urology, from the "Prof. dr. Th. Burghel" Hospital, Bucharest, for one month intermittent hematuria. Ultrasonography showed a sessile tumoral mass, sized 37/30mm. Transurethral resection of the tumor mass was performed and tissue fragments were sent to the pathologic lab to establish the histologic type, the degree of differentiation and invasion. Fragments of the tumor were fixed in 10% formaldehyde, paraffin embedded and processed as standard technique; the sections were stained with HE, VG and immunohistochemically with: CROMO, EMA, NSE, CD56, NK1, p53 and β HCG. The microscopic examination revealed a tumor proliferation composed of two distinct components: extensive small cells areas and foci of typical low grade (G2) papillary urothelial carcinoma. The small cell are uniformly, round, with increased nucleo-cytoplasmic ratio, eosinophil cytoplasm, hyperchromatic nuclei, finely granular chromatin and inconspicuous nucleoli. Immunohistochemical stains showed diffuse positive staining of the small cell component for CROMO, EMA, NSE, CD56, NK1 and urothelial carcinoma component stained focally for β HCG. The rate of cell proliferation was increased (p53 – 80% positive reaction). *Conclusions.* A diagnosis of small cell carcinoma coexisting with low-grade urothelial carcinoma was established. Because of aggressive behavior and distinct treatment, the pathologist should watch out for the presence of small cell carcinoma component.

Keywords: small cell carcinoma, urinary bladder, urothelial carcinoma, immunohistochemistry.

Introduction

In 1981, Cramer SF has described the first case of small cell carcinoma of the urinary bladder (SCCUB) [1].

Small cell carcinoma usually involve male patients (male/female ratio 6–7 : 1) and accounts for less than 1% of all cancers arising in the urinary bladder [2–3].

Neuroendocrine carcinoma comprises carcinoid tumors, large cell neuroendocrine carcinomas and small cell carcinomas [4, 5].

Among neuroendocrine tumors of the urinary bladder, small cell carcinomas are most common with more than 100 cases having been described until now. Like small cell, carcinoma of the lung (SCLC) this entity has the same histopathological and immunohistochemical features. After Shahab N *et al.* (2007), risk factors are unknown but there are hypothesis that cigarette smoking, bladder calculi and long-term cystitis are involved in pathogenesis [6].

The survival is only few month because most of the patients have metastatic disease [7].

Current diagnosis and management are often patterned after SCLC but the therapy is different. For example, many patients with SCCUB undergo local resection, which is rarely performed in SCLC [4].

Unfortunately, the optimal management is not well defined; therapeutic modalities vary and include transurethral resection, cystectomy, radiation therapy and systemic chemotherapy [8].

Fifty percent of cases are associated with urothelial carcinoma, usual type or metaplastic, adenocarcinoma and squamous cell carcinoma, sarcomatoid or a mixture of carcinomatous components.

Histogenesis of this disease is unknown: there are hypothesis that sustain urothelial origin, other who sustain malignant transformation of neuroendocrine cells of urinary bladder and the stem cell theory [6].

The involvement of cytogenetic or others molecular changes are not well known [7]. The mean age of patients presenting with SCCUB is 66 years (range 36 to 85). Presenting symptoms include hematuria, dysuria, obstructive voiding symptoms, weight loss,

abdominal pain, urethral obstruction with flank pain and recurrent urinary tract infection [9].

Macroscopically, these tumors may appear nodular, polypoid, sessile, ulcerated and/or infiltrative. Usually are large and arise from all regions of the urinary bladder including in diverticula. The mean size for SCCUB is 5.1 cm (range 1.5 to 13 cm) and the most tumors arise in the lateral and posterior walls [10].

Histologically, SCCUB comprises sheets of uniformly small, round, mitotically active cells with overlapping nuclei, lacking prominent nucleoli, nuclear molding and tumor necrosis. SCCUB has been associated with paraneoplastic syndromes [10].

We report a new case of SCC of urinary bladder associate with low-grade urothelial carcinoma and discuss relevant current literature.

Our patient was a 44-years-old man, smoker, without other co-morbidities, hospitalized for one-month intermittent gross hematuria.

Ultrasonography and cystoscopic examination revealed a sessile tumoral mass. Transurethral resection of the tumor mass was effected and tissue fragments were sent to the Pathology Department to establish the histological type, the degree of differentiation and invasion according to the 2004 TNM system and WHO stage grouping. Others clinical investigations (CT, pulmonary X-ray, RMN) established that our case is free of metastasis.

After four months, follow up cystoscopy was done at the same location for the biopsy and the pathologic examination showed cystitis features.

Material and methods

Macroscopically there was a sessile tumoral mass, sized 37/30 mm, located on the antero-lateral right wall of the urinary bladder.

Many tissue samples obtained during transurethral electro resection were fixed in 10% formaldehyde, paraffin-embedded, sectioned and standard HE and VG stained then examined by light microscopy (Nikon Eclipse E 600) using the 2004 TNM system and WHO stage grouping for bladder tumors. Representative photomicrographs were taking using Nikon Plan 20 \times and 40 \times .

Immunohistochemistry was performed on 3 μ m thick sections from 10% formalin fixed paraffin-embedded specimens, according to the avidin–biotin complex method of the tissue [11], modified by Bussolatti G and Gugliotta P [12], Miller K [13], and Ardeleanu Carmen *et al.* [14].

Briefly, the procedure was: deparaffinization in xylene and alcohol series rehydration, washing in phosphate saline buffer (PBS), incubation with normal serum for 20 minutes incubation with primary antibody overnight, standard labeled streptavidin–antibody biotin (LSAB) kit (DAKO), washing in carbonate buffer and development in 3,3'-DAB hydrochloride/H₂O₂.

Selected tumoral fragments were tested by the following antibodies: CROMO 1:50 (Novokastra, UK), EMA 1:75 (Dako, Denmark), NSE 1:100 (Dako, Denmark), CD56 1:50 (Neomarkers, USA), NK1 1:50

(Dako, Denmark), p53 1:50 (Dako, Denmark), β HCG 1:500 (Novokastra, UK).

All specimens were counterstained with Mayer's Hematoxylin, examined and photographed on a Nikon Eclipse 600 microscope.

Results

The histopathological features showed a tumor proliferation composed of two distinct components: extensive small cells areas (Figure 1) and foci of typical low-grade papillary urothelial carcinoma.

The small cells were uniformly, round, with increased nucleo-cytoplasmic ratio, eosinophil cytoplasm, hyperchromatic nuclei, finely granular chromatin and inconspicuous nucleoli. The cytoplasm was scanty with molding of nuclei.

Foci of typical low-grade (G2) papillary urothelial carcinoma (Figure 2) were composed of multiple layers of cells who have acidophilic cytoplasm, elongated nuclei with finely granular chromatin.

The tumor appeared to have invaded *lamina propria* of the urinary bladder. The stage was pT1N0M0 according to the 2004 TNM system and stage according to WHO stage grouping.

Immunohistochemical profile emphasized:

- NSE diffuse positive staining of the small cell component (Figure 3).
- EMA diffuse positive reaction in small cell areas (Figure 4).
- CROMO low positive reaction in rare tumor cells (Figure 5).
- CD56 positive reaction in tumor cells.
- NK1 positive reaction in tumor cells (Figure 6)
- Urothelial carcinoma component stained focally for β HCG, in these areas neuroendocrine tumoral markers were negative (Figure 7).
- The rate of cell proliferation was increased: p53 – 80% positive reaction in tumor cells (Figure 8).

Discussions

Among the many site for primary small cell carcinoma is the genitourinary tract. According to literature data, the majority of cases have been observed in the bladder and prostate [6]. It is now believed that the small cell carcinoma of the bladder originates from the totipotent stem cells present in the submucosa of the bladder wall [6].

A number of chromosomal aberrations have been reported in small cell cancer of the bladder. There are no specific clinical features differentiating these patients from transitional carcinoma of the bladder. The most common symptomatology is hematuria [15].

Cancer registration statistics of economically advanced countries indicate that bladder carcinoma incidence ranks fourth in men and eight in women, but a reliable tumor marker for predicting the disease course is still lacking [16]. The tumor histology is characteristic on low power light microscopic examination with a diffuse, pattern less arrangement of round, blue hyperchromatic cells interspersed with areas of focal necrosis.

Figure 1 – Small cell carcinoma component (HE staining, ob. ×10)

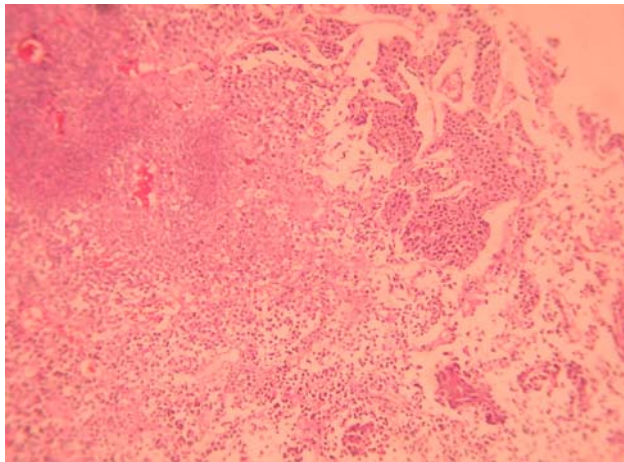
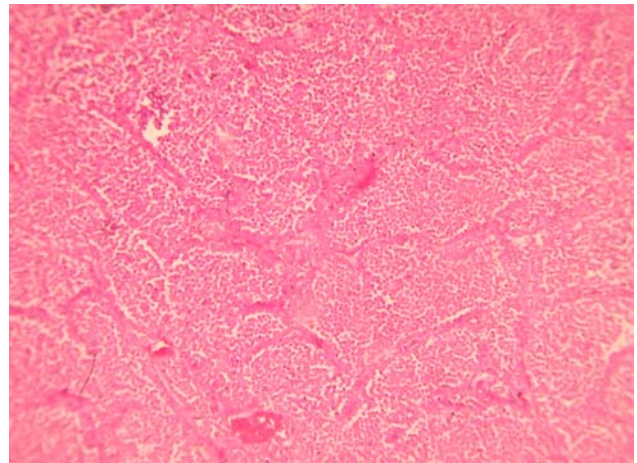


Figure 2 – Transitional low grade papillary carcinoma component (HE staining, ob. ×10)

Figure 3 – NSE diffuse positive staining of the small cell component (ob. ×10)

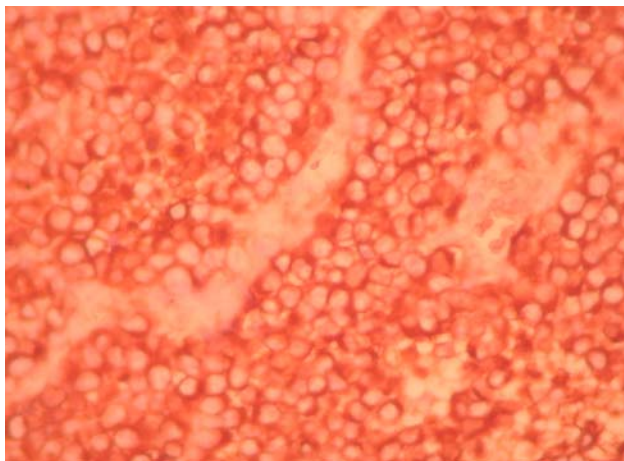
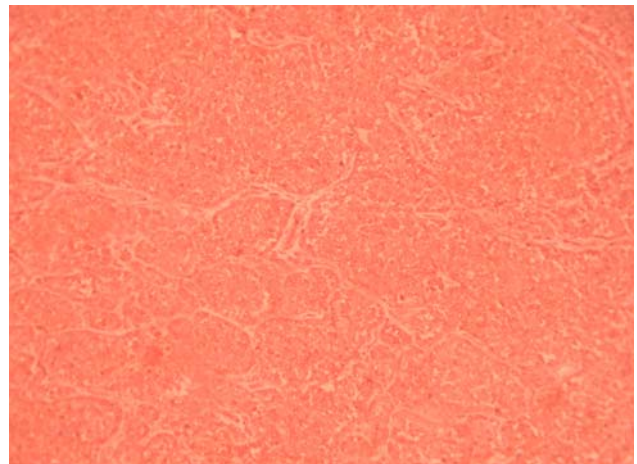


Figure 4 – EMA diffuse positive reaction in small cell areas (ob. ×40)

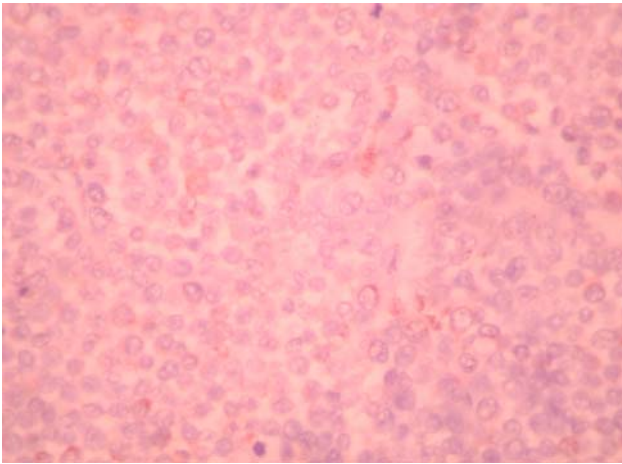


Figure 5 – *CROMO* low positive reaction in rare tumor cells (ob. $\times 40$)

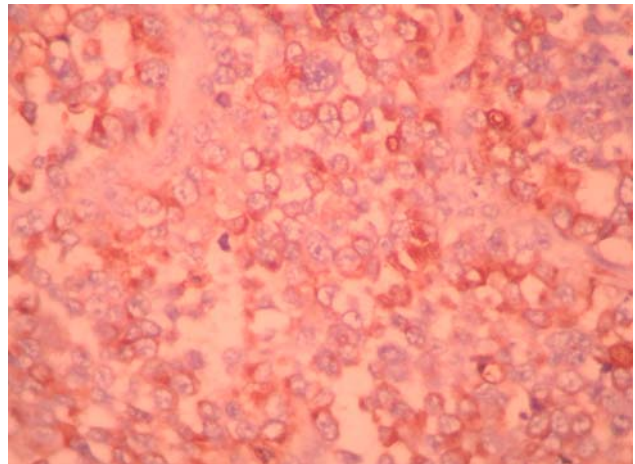


Figure 6 – *NK1* positive reaction in tumor cells (ob. $\times 40$)

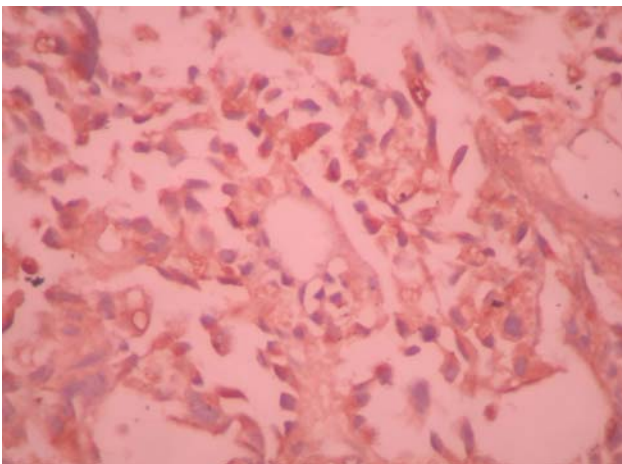


Figure 7 – Urothelial carcinoma component stained focally for β HCG (ob. $\times 40$)

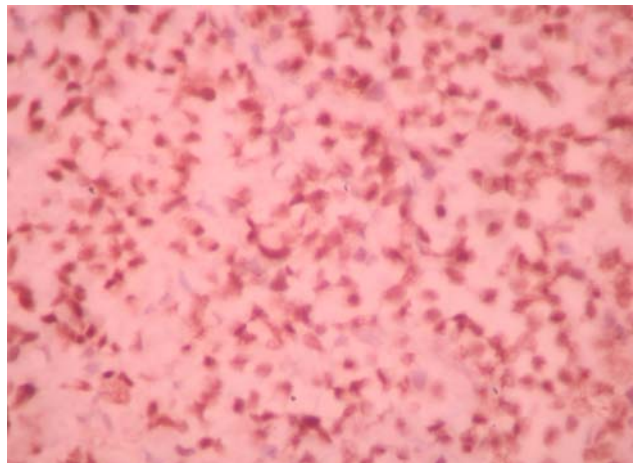


Figure 8 – *P53* 80% positive reaction in tumor cells (ob. $\times 40$)

The cells have granular chromatin, inconspicuous nucleoli and frequent mitoses. The tumors are widely invasive and involve muscle [15].

Although many immunohistochemical antibodies have been reported in small cell carcinoma of the bladder, from a diagnostic perspective, chromogranin, NSE, synaptophysin and cytokeratin (often dot-like positivity) are usually sufficient [15].

We report the case of a primary small cell carcinoma of the urinary bladder coexisting with low-grade papillary urothelial carcinoma component. The differential diagnosis is vast and included a high-grade urothelial carcinoma (some of them have smaller cells and a diffuse growth pattern but IHC tests help us to put the right diagnosis), lymphoma, metastatic lesions, especially from the lung, carcinoid, lympho-epithelial like carcinoma, plasmocytoid carcinoma [16, 17].

Lymphomas of the bladder are rare; the cells are small but usually preserve the architecture of the bladder and are widely invasive [17].

The nuclear features are distinct from SCC. It is crucial importance to recognize it because the bladder lymphomas treatment is different, survival is prolonged and have a good prognosis with a good response to chemotherapy. Immunohistochemical stains allow us to distinguish these possibilities.

The features of metastatic small cell carcinoma of lung origin are indistinguishable from primary small cell carcinoma of the bladder on the bases of histology alone [15].

However, the presence of a low-grade urothelial carcinoma in our case was suggestive evidence of a primary bladder lesion and the X-ray of the lung did not describe any lesion. A more problematic situation is to rule out a direct extension of a small cell carcinoma from the prostate gland or uterus, but prostate specific antigen or prostate specific acid phosphatase staining in the better differentiated are helpful [10].

The true incidence of this entity in the urinary bladder may be underreported if the diagnosis is not considered and the appropriate diagnostic methods are not carried out. Although bladder neuroendocrine carcinoma is an aggressive tumor, the prognosis is better than those patients with neuroendocrine carcinoma of other sites [17].

Because the optimal management of this tumor is not very well defined, after discussions between oncologist, pathologist and surgeon the patient was proposed for radical cystectomy. Small cell carcinoma of the urinary bladder therapy is different from that for the small cell carcinoma of the lung [4].

Cheng L *et al.*, 2004, showed no significant survival between patients who did and did not undergo cystectomy [16].

Holmang S *et al.*, 1995, revealed that primary small cell carcinoma of the bladder is less aggressive than the pulmonary small cell carcinoma and that some patients can be cured by transurethral resection, partial or radical cystectomy combined with radiotherapy [18].

Some studies showed that cisplatin-based chemotherapy appears to have a better survival and

prognosis [6, 19]. The Mayo Clinic experience revealed that treatment is stage-dependent: patients with stage II achieved a cure with radical cystectomy, stage IV and III disease treated with chemotherapy [20, 21].

Despite improved outcomes in treating small cell carcinoma, the prognosis remains dismal. According to WHO, poor survival predictors are age greater than 65 years, high TNM stage and metastatic disease. This cancer is often detected in an advanced stage. Survival rates are stage dependent but in general are low. Other suggests there is no correlation between survival rate and stage. Median survival for all the patients is 20 to 23 months and five-year disease specific survival rates vary from 16 to 40% [8].

Urothelial carcinomas may produce hormones, the most common of which is beta-human chorionic gonadotropin (β HCG). We found focally positive reaction for β HCG in urothelial carcinoma component. Hormone immunoreactivity was frequently observed in highly proliferating areas [9]. Normal urothelium, urothelial papillomas and carcinoma in situ showed no positive reactions [9]. Recent structural and clinical studies suggest that this hormone might act as local tumor growth factor.

Conclusions

Small cell carcinoma of the urinary bladder is a distinct histological and biologic disease entity with an aggressive clinical course, poor prognosis and average life expectancy of only few months.

The light microscopic diagnosis of SCCUB can be challenging, the diagnosis is supported by positive immunostaining for chromogranin, NSE and NK1 (CD57) and has prognostic and therapeutic implications.

Therapeutic modalities vary from institution to institution and include transurethral resection, as well as combinations of cystectomy, radiation therapy and systemic chemotherapy. Because of aggressive behavior and distinct treatment, the pathologist should watch out for the diagnosis of primary pure small cell carcinoma of the urinary bladder or presence of small cell carcinoma component in cases associated with other types of cancer.

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