Large Cell Neuroendocrine Carcinoma of the Urinary Bladder: Case Report and Review

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Abstract
Introduction: Neuroendocrine carcinomas of the urinary bladder are relatively rare, accounting for less than 1% of all bladder carcinomas. These tumors can be divided into the more indolent typical or atypical carcinoid tumors and the aggressive small cell and large cell neuroendocrine carcinomas. Objective: To report 2 clinical cases of large cell neuroendocrine carcinoma of the bladder (LCCB) and to review the epidemiology, prognosis, and current treatment algorithms for patients with bladder small and large cell neuroendocrine carcinomas. Results: In both cases hematuria was the presenting symptom. One patient was submitted to partial cystectomy and the other to trans-urethral resection of the bladder tumor. The former patient died on the third month postoperatively. The latter patient had extensive liver metastasis at the time of diagnosis and died from acute liver failure on the 14th postoperative day. In review LCCB is associated with a more aggressive behavior and poorer prognosis than transitional cell bladder carcinoma. No standard approach exists. Surgery (transurethral resection, partial cystectomy, radical cystectomy), chemotherapy and radiotherapy are current treatment modalities. Conclusion: LCCB is an aggressive tumor which usually presents itself in an advanced stage. Neoadjuvant chemotherapy with platinum regimen plus aggressive surgical approach should be the treatment of choice.

Introduction

Neuroendocrine carcinomas of the urinary bladder are relatively rare, accounting for less than 1% of all bladder carcinomas [1]. These tumors can be divided into the more indolent typical or atypical carcinoid tumors and the aggressive small cell and large cell neuroendocrine carcinomas.

Small cell carcinoma of the urinary bladder (SCCB) was first recognized in 1981 [2] and further 550 cases have been reported on the literature up to 2007 [3]. Large cell carcinoma of the urinary bladder (LCCB) was first reported in 1986 [4] and since then 17 more cases have been described on the literature [5–16]. Because of the relative rarity of these tumors there is no standard approach for managing SCCB [17] or LCCB [13].

In many cases SCCB and LCCB co-exist with a distinct additional carcinomatous component, including transitional cell carcinoma, adenocarcinoma and sarcomatoid urothelial carcinoma [1]. We report 2 cases of patients with LCCB which were treated in our urology department over a period of roughly 5 years.

Case Reports

Case 1

A 79-year-old man with a history of hypertension, dyslipidemia, benign prostatic enlargement, asthma and stroke was admitted to our urologic department on the account of hematuria which did not resolve with medical treatment. He was submitted to a diagnostic cystoscopy that revealed a large mass on the left lateral and anterior wall. Taking into account the age and comorbidities of the patient, it was decided to perform a partial cystectomy. The postoperative period was complicated by the presence
of urinary fistula (documented by high levels of creatinine in the fluid drainage) and infection of the surgical wound. These complications were however managed with conservative measures and there was no need to re-operate the patient. A cystography done later showed no urinary leaks. The patient was discharged on the 32nd postoperative day.

The pathology report revealed a large cell neuroendocrine bladder tumor, with focal areas of adenocarcinoma, micropapillary carcinoma and squamous cell carcinoma which accounted for less than 2% of the tumor total volume. The tumor invaded deeply into the bladder fat (pT3). Synaptophysin, chromogranine A and CD56 immunohistochemical markers were positive especially in the most undifferentiated areas of the tumor.

A postoperative abdomino-pelvic CT scan showed heterogeneity of the fat close to the left lateral and anterior bladder wall, probably related to the surgical exploration and posterior infectious complications, several lymphadenopathies on the left iliac arteries, and no apparent distant metastasis.

The patient was scheduled to begin adjuvant chemotherapy with cisplatin and etoposide but before he could start the treatment he had new episodes of hematuria and worsening of the general status which delayed the beginning of the chemotherapy. He would eventually pass away roughly 3 months after surgery before beginning any adjuvant treatment.

Case 2
A 37-year-old man was referred to our urology department because of macroscopic hematuria, which had begun 3 months earlier and persistent storage lower urinary tract symptoms. The clinical history was unremarkable and the patient had no history of cigarette smoking. An abdominal ultrasound was performed revealing a suspicious mass addressing the bladder anterior wall and fundus with about 5 cm. Several hypoechoic nodules in the liver were also detected. A staging abdomino-pelvic CT scan was performed later, which revealed multiple hypovascular nodules in the liver suggesting liver metastasis (the largest with 10 cm diameter), a 3 x 6 cm vesical mass which contacted with colon and a 2.7 x 2.3 cm lymphadenopathy neighboring the obturator vein.

The patient was submitted to a diagnostic trans-urethral resection of the bladder tumor. The immediate postoperative period was uneventful but later on he developed crippling perineal pain because it was hypothesized that they originated from the neuroendocrine with non-neuroendocrine carcinomas of the bladder developed from Kulchitsky cells. Later it was hypothesized that they originated from the neuroendocrine amine precursor uptake and decarboxylation system within the transitional epithelium or as a result of urothelial metaplasia. Actually it is now believed that SCCB arises from totipotent stem cells of the submucosa of the bladder wall, which explains the frequent association of neuroendocrine with non-neuroendocrine carcinomas [4, 5, 23].

Neuroendocrine Carcinoma of the Bladder: Review

Bioendocrine Carcinoma of the Bladder appears frequently in the respiratory and gastrointestinal tract. SCCB is the most common of the primary genitourinary neuroendocrine tumors, although it accounts for less than 1% of all primary bladder tumors [18, 19]. It is a disease with a male predominance, usually affects older patients [17, 19] and is related to a smoking history [17].

Neuroendocrine tumors can be classified into 4 major histological categories: low grade malignant “typical” carcinoids, intermediate grade malignant “atypical” carcinoids and 2 high grade tumors – small cell carcinoma and large cell carcinoma. This classification arose mainly from the clinical experience with lung neuroendocrine tumors. As far as the bladder is concerned SCCB was first recognized in 1981 [2], LCCB was first reported in 1986 [4] and since then 17 more cases have been described in the literature [5–16].

Neuroendocrine carcinomas of the bladder appear as pure or composite tumors where the neuroendocrine component (small cell or large cell) is commonly associated with urothelial cell elements. To this day there is no correlation between different ratios of neuroendocrine and non-neuroendocrine components in bladder carcinoma with outcome or response to therapy [20].

Neuroendocrine large cells carcinoma is characterized by large, polygonal cells, with a low nuclear/cytoplasmic ratio. Coarse chromatin and frequent nucleoli, mitotic activity in excess of 10 mitoses per 10 high power fields and multiple areas of necrosis are also common [11].

Immunohistochemical markers commonly used to demonstrate neuroendocrine differentiation, such as chromogranin, synaptophysin and neuron-specific enolase are variably expressed in SCCB [21] and can be also present in LCCB [11]. Thyroid transcription factor-1 can also be present in SCCB and LCCB [11]. Cytological findings in urine samples of patients with SCCB are distinctive and an accurate diagnosis can be made. Differential diagnosis includes metastatic small cell carcinoma, high grade transitional cell carcinoma and malignant lymphoma. Lymphoma is by far the closest mimicker of SCCB in urine cytology [22].

Initially it was believed that neuroendocrine carcinomas of the bladder developed from Kulchitsky cells. Later it was hypothesized that they originated from the neuroendocrine amine precursor uptake and decarboxylation system within the transitional epithelium or as a result of urothelial metaplasia. Actually it is now believed that SCCB arises from totipotent stem cells of the submucosa of the bladder wall, which explains the frequent association of neuroendocrine with non-neuroendocrine carcinomas [4, 5, 23].
In an analysis of 238 patients with SCCB mean patient age at diagnosis was 67.8 years and 80% of the patients were male [24]. Hematuria is usually the presenting symptom [24] and rarely paraneoplastic syndromes may herald the diagnosis [25, 26].

In a retrospective study which included 44 patients with SCCB and 2 patients with LCCB, SCCB prognosis and survival is closely related with stage at diagnosis, as opposed to his lung counterpart. In fact TMN stage was the only prognostic factor with a statistical significant relationship to survival [11]. The outcome was also relatively better for SCCB than for small cell lung carcinoma. However in a study with 25 patients with SCCB the difference in survival between those with limited and extensive disease was not statistically significant, although the statistical power to detect a difference was limited by the small numbers of patients in each group [27]. Furthermore in a larger retrospective analysis of genito-urinary small cell carcinoma which included 106 patients with SCCB, tumor stage was not independently associated with survival, suggesting that micrometastases are often present concurrent with clinically localized disease [18].

The optimal treatment strategy for these patients is not known. Surgery, chemotherapy and radiotherapy have all been used either alone or as a multimodality therapy. Because of the rarity of these tumors, no prospective trials have been done to evaluate the optimal treatment [28].

There is evidence that that SCCB of the bladder should be considered as a systemic disease. In fact SCCB usually presents with metastatic disease (40–90% depending of the series) [18, 29, 30]. There are a few reports of patients with localized disease who were submitted to trans-urethral resection of the bladder or radical cystectomy with survival exceeding 5 years [23, 29–32]. Most of these patients were submitted to adjuvant external beam radiotherapy. However the treatment strategies that have focused on local therapy have had disappointing results. Mackey et al. [18] reported a median survival of 13 months in their review. Holmang et al. [29] reported a 28% survival rate at 19 months in 18 patients with cystectomy and radiotherapy. Abbas et al. [26] found that 73% of patients were alive at a mean follow-up of 21 months when cystectomy was combined chemotherapy.

Patients receiving multimodality therapy including chemotherapy with platinum-based therapy have a significantly better outcome. Quek et al. [9] reported that patients receiving multimodality therapy including chemotherapy with cisplatinum had significant better overall and recurrence-free survival than those treated with cystectomy alone. There was no significant survival difference between SCCB and LCCB in this study. In another study chemotherapy was an independent prognosticator for survival when corrected for stage [27]. In a larger retrospective study, metastatic disease predicted a poor outcome and cisplatin therapy, not surgery improved survival [18]. While it is difficult to directly compare the outcome between the small reported series, the addition of neoadjuvant and adjuvant combination chemotherapy to cystectomy appears to provide a survival advantage [24].

**Discussion**

Bladder cancer is the second most common urologic malignancy. In the western countries, it is the fourth most common cancer in men and the eighth most common cancer in women [33]. Up to 95% of urinary bladder tumors are of epithelial origin, from which 90% are urothelial neoplasms [34]. Primary SCCB is a rare disease that accounts for less than 0.7% of all bladder cancers [29, 30]. Primary LCCB is an even rarer disease first described in 1986 [4] and with 17 more cases reported since then [5–16].

The 2 clinical cases presented in this article attest the fact that bladder neuroendocrine tumors are a high grade malignant carcinoma with a poor prognosis because of their high metastatic potential.

When we look at the available literature, we can see that Abenoza et al. [4] and Hailemariam et al. [5] reported the first cases of LCCB in 1986 and 1998, respectively. Both patients were men. The first tumor presented mixed histology with adenocarcinoma while the latter presented a pure LCCB. Both patients were treated with radical cystectomy and bilateral lymphadenectomy. Both patients died of the disease (30 and 2 months post operation respectively).

Dundr et al. [7] and Li et al. [8] report single cases of 1 woman and 1 man with 54 and 61 years of age submitted to radical cystectomy. The former patient was alive at 16 months with lymph node metastasis and the latter was alive without disease at 8 months follow-up.

Bertaccini et al. [13] report a case of a 37-year-old man with a 2.5 x 2cm posterior bladder wall LCCB who underwent radical cystoprostatectomy with orotopic neo-bladder reconstruction, pelvic lymphadenectomy and adjuvant chemotherapy with carboplatin and etoposide. The patient was still alive and without evidence of local or systemic recurrence 22 months after surgery.
Evans et al. [6] report a case of a primary large LCCB, with an admixed minor element of adenocarcinoma, in an 82-year-old man. The patient underwent a partial cystectomy with left-sided pelvic lymphadenectomy. The patient developed a local recurrence 8 months postoperatively, which was managed by a combination of transurethral resection and radiation therapy. There was no evidence of local or metastatic disease 2 years after initial diagnosis.

Lee et al. [10] report a case of LCCB in a 32-year-old man treated with partial cystectomy and adjuvant chemotherapy. Metastasis at lung and liver was present 12 months after surgery while the other was alive without disease at the 13th month post-operatively. They report a similar clinical behavior of LCCB when comparing with SCCB.

Quek et al. [9] present a series of 25 patients with neuroendocrine tumors treated with radical cystectomy. Five of these patients had a LCCB, in which 4 of them presented with advanced disease (lymph node positive) and overall survival was poor (only 1 patient survived more than 2 years). No apparent difference in overall or recurrence-free survival was appreciated between LCCB and SCCB.

Lee et al. [14] and Tsugut et al. [16] reported 2 cases of diagnosis of LCCB after discovery of cutaneous metastasis and brain metastasis, respectively.

As such LCCB is a rare and aggressive disease. Although the overall prognosis is poor and most patients present with metastatic disease, there are few reports of successful treatment in patients with limited disease subjected to a multimodal approach including aggressive surgical treatment and adjuvant chemotherapy.

Still treatment modalities (surgery, chemotherapy and radiotherapy) are not well defined because of the rarity of these tumors. A potential benefit of adjuvant chemotherapy has been suggested. Thus, treatment of disseminated forms is based on chemotherapy with platinum. Treatment of localized forms has to take account of the high frequency of micro-metastasis and is based on a combination of chemotherapy to radical surgery or radio-chemotherapy.

**Conclusion**

Similar to SCCB, LCCB is an aggressive tumor which usually presents itself in an advanced stage. The prognosis is grimmer than urothelial bladder cancer. In the absence of prospective studies, no standard approach exists. For localized disease, aggressive surgical treatment and adjuvant chemotherapy can lead to lasting overall and disease-free survival. For metastatic disease, the chemotherapy using a platinum agent is the mainstay treatment.

**References**

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