# Diagnosing Small Cell Carcinoma of the Bladder

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**Abstract.** Small cell carcinoma of the urethra (SCCB) is a rare yet highly aggressive malignancy. The pathogenesis of SCCB is poorly understood due to few large-scale cohort studies. Currently, SCCB is diagnosed primarily by morphological assessment. However, immunohistochemical staining can also play an important role, particularly in cases that are difficult to distinguish morphologically. In this study, we described an 85-year-old male who suffered from discontinuous gross hematuria and odynuria. He underwent transurethral resection of the bladder tumor for imaging identified mass with the final diagnosis SCCB after morphological and immunohistochemical assessments. And we observed that immunohistochemical staining played an important role in the diagnosis of SCCB, especially in cases that were difficult to distinguish based on morphology alone.

## Introduction

Urinary bladder cancer is the fourth most commonly seen malignancy within males in the United States. It was expected that 56,390 newly diagnosed cases and 11,170 deaths will be reported in 2014 [1]. Bladder cancer is categorized into two major groups according to their sites of origin [2]: urothelial carcinoma (UC) and non-urothelial epithelial malignancies,. The latter consists of squamous cell carcinoma, adenocarcinoma, neuroendocrine carcinoma and small cell carcinoma. These malignancies contribute to less than 10% of all bladder cancers. Among them, small cell carcinoma of the bladder (SCCB) is rarer and accounts for only 0.7% of all cases[3].

SCCB is well known for its highly aggressive nature. It is characterized by early metastasis, short survival times and high mortality rates. Prior cohorts reported median survival times of 3 to 33 months, regardless of treatment [3,4]. Therefore, understanding this disease, including pathogenesis and accurate diagnostic strategies, is

 

very important. Unfortunately, current data, as demonstrated in the Surveillance, Epidemiology, and End Results (SEER) database analysis, has provided rather limited amount of cases available for study [3].

To date, the diagnosis of SCCB mainly relies on morphological evaluation with microscope [2]. Typically, SCCB presents as small uniform cells with frequent nuclear molding, inadequate cytoplasm, and finely stippled chromatin [2]. However, a common mixture of other more favorable epithelial components, such as transitional cell carcinoma and squamous cell carcinoma, may often lead to misdiagnosis. Moreover, the equivocal origin of SCCB increases diagnostic difficulties. Hence, though World Health Organization criteria allows microscopic assessment in the diagnosis of SCCB [2], novel immunohistological biomarkers, such as neuroendocrine markers and cytokeratins, are also recommended for decision making. In order to examine the application of various immunohistochemical strategies to correctly diagnose SCCB, we presented a case in which an 85-year-old male underwent transurethral resection of the bladder tumor (TUR-BT) and was diagnosed with SCCB after morphological and immunohistochemical assessment.

## Case Report

An 85-year-old male was admitted to the Department of Urology, China-Japan Union Hospital of Jilin University with discontinuous gross hematuria within the past three months, as well as anorexia, weight loss and odynuria within the past month. Personal and medical history review revealed a history of smoking for more than 50 years, cerebellar atrophy for ten years, angina pectoris for six years, and hypertension for five years. The patient's blood pressure was well controlled with regular oral hypotensor, however, the patient's angina was not systemically treated. No prior history of HPV infection or cancer was detected. A routine urine test showed normal white blood cell counts, red blood cell (RBC) counts, and total urine protein. A blood test revealed anemia, with decreased RBC of $3.22\times10^{12}$/L and hemoglobin of 97 g/L. Elevated blood urea nitrogen (9.20 mmol/L), elevated creatinine (156.80 μmol/L), and decreased retinol conjugated protein (1.28 mg/L) were also detected. Liver function was normal.

Urinary system ultrasonography demonstrated a high echogenic mass with potential bleeding in the bladder. Abdominal computed tomography (CT) scan indicated that a cauliflower-like mass of 2.7 cm × 2.2 cm was located at the upper-posterior wall of the bladder . The lesion also presented with an unclear boundary, heterogeneity, and some areas of high-density mottling (CT values of 35-86 Hounsfield Units). No adjacent viscera metastases or enlarged lymph nodes were detected. Magnetic Resonance Urography (MRU) showed a similar presentation of the bladder as in the CT imaging. Normal kidney and ureter were observed. Electrocardiogram revealed myocardial ischemia and echocardiography found dyskinetic left ventricle (ejection fraction 68%), left ventricle diastolic dysfunction, aortosclerosis, and mild mitral and aortic valves regurgitation.

After obtained normal RBC counts with blood transfusion, the health care team decided to perform TUR-BT patient's physical condition did not allow for extensive chemotherapy. Surgical procedures were carried out per the institution's protocol. After surgery, irrigation of the bladder with 20 mg hydroxycamptothecine was performed to prevent tumor pervasion. The patient tolerated all procedures well. Intro-operative specimens, including a mass of 3.0 cm × 2.5 cm × 1.5 cm, a deep muscle layer and

adjacent normal tissues (thickness ~0.5 cm) were submitted to pathological analysis with a diagnosis of SCCB.

Electron microscopy (hematoxylin-eosin staining) results were as followed: i) the tumor had a patternless type of diffuse growth and cell nests were observed; ii) tumor cells were round or oval in shape with evenly scattered salt-and-pepper-like chromatin; and iii) mitosis and necrosis were commonly seen. Immunohistochemical stains were positive for CD56, Chromogranin A (CGA), Synaptophysin, Thyroid Transcription Factor 1 (TTF-1), Ki67 (90%), and PAX-5. The tumor was focally positive for CK20, CK7, and P504S, and was negative for prostate-specific antigen, Transformation-related protein 63 and leukocyte common antigen (LCA) . Post-operative tumor staging was $T_1N_0M_0$ according to the American Joint Committee on Cancer (AJCC) TNM Staging System for Bladder Cancer ($7^{th}$ ed., 2010). Unfortunately, the patient suffered from a sudden heart attack ten days after surgery and died before further treatments could be considered.

All information was collected from the medical history database in our institution. The Institutional Review Board of China-Japan Union Hospital of Jilin University approved the case report.

## Discussion

Small cell carcinoma of the bladder (SCCB) is an extremely rare malignancy. The understanding of its pathogenesis has been extremely limited for the past several decades. Several hypotheses have been proposed regarding the origin of SCCB. However, none can completely explain the behavior of this heterogeneous disease. Sidhu reported that SCCB resembled amine precursor uptake and decarboxylation cells and may be of endodermal origin [5]. A study carried out by Ali et al. [6] suggested that some SCCB cells presented neuroendocrine features and may be a malignant transformation of neuroendocrine cells. Nonetheless, Blomjous et al. [7] reported that SCCB originates from multipotent mucosal stem cells, providing that the aggressiveness of the tumor was independent from neuroendocrine differentiation characteristics in both immunohistological and microscopic studies. They also showed that SCCB cells were capable of differentiating into various human tissues. The last theory offered the best explanation for the frequent mixture of SCCB with other malignancies (transitional cell carcinoma, squamous cell carcinoma and adenocarcinoma) and also illustrated the aggressive nature of SCCB.

Due to the controversial origin of SCCB, biomarkers have been tested to properly diagnose SCCB and to differentiate SCCB from other malignancies. For example, poorly differentiated UC, which often co-exists with SCCB, can be mistaken for SCCB. Among the recognized immunohistochemical staining strategies, neuroendocrine markers were commonly used. CGA is a neuroendocrine secretory protein found in about 30% of SCCB cases but in only 5% of bladder UC cases. Therefore, this marker can be used in the differential diagnosis of SCCB and UC. Buza et al. [8] demonstrated that Synaptophysin and CD56 were expressed in SCCB. However, CD56 was more prevalent than Synaptophysin (71.4% vs. 64.3%). Synaptophysin is a major synaptic vesicle protein in neuroendocrine cells and is associated with synaptic activity. CD56, a transmembrane glycoprotein expressed on various types of cells, is essential for cell

adhesion, synaptic plasticity and neuron growth. In our work, immunohistochemical staining revealed positive CGA, Synaptophysin and CD56. This staining pattern suggested a diagnosis of SCCB.

TTF-1, also known as NK2 homeobox 1, is a transcriptional factor expressed in thyroid follicular cells and small cell lung cancer, and was proposed to be a potential marker for the latter. However, the specificity in small cell lung cancer has long been questioned. Jones et al. [9] observed that the expression of this factor was not restricted to pulmonary lesions. It was also found in 39% of SCCB cases, while none of the concomitant urothelial component presented positive results. However, they also reported that TTF-1 did not correlate with the clinicopathological characteristics in SCCB, suggesting the potential limitation of TTF-1 in diagnosing SCCB. However, we detected positive TTF-1 staining in this study, confirming the possible expression of this factor in SCCB. However, further characterization is needed to determine whether TTF-1 is a reliable diagnostic biomarker for SCCB.

Transformation-related protein 63 (TP63) is a transcription factor that is critical for epidermal development. It is a typical marker of high grade UC and absent in SCCB. Similarly, CK20, a cytokeratin involved in urothelial dedifferentiation, is a potential prognostic factor and reliable indicator of biologic aggressiveness for pT1 UC, while it was found to be only focally positive in 14.3% of SCCB cases [8]. Another member of the cytokeratin family, CK7, is highly expressed in high grade UC (81.3%) [8]. Therefore, these immunohistochemical markers are beneficial in differentiating SCCB and UC. Accordingly, we observed negative staining of TP63, and focally positive staining of CK20 and CK7.

Some malignancies of prostate origin, especially small cell carcinoma of the prostate (SCCP), can morphologically resemble SCCB. Therefore, staining for prostate markers should be taken into consideration to provide an accurate diagnosis. Positive prostate-specific antigen (PSA) staining indicates the presence of prostate adenocarcinomas (though PSA staining is sometimes negative in SCCP). P504S, a cytoplasmic protein, can also detect prostate carcinoma. Jiang et al. [10]reported that P504S showed strong cytoplasmic granular staining in 100% of prostate carcinoma cases and was negative in 88% of benign prostate tissue. Others presented similar results that P504S was best when employed together with strict light microscopic correlation. We observed negative PSA staining and focally positive P504S staining in our case, demonstrating that the tumor did not originate in the prostate.

PAX-5 (B-cell-specific activator protein) is a marker of B cells and plays a pivotal role in B-cell ontogeny. But at the meanwhile, it is also found to be positive in small cell carcinomas. Our data provided evidence that PAX-5 was positive in this case, supporting the diagnosis of small cell cancer other than UC. We also ruled out hematopoietic neoplasms, given that LCA staining was negative.

Currently, the recommended treatment for SCCB is chemotherapy (similar regimens used to treat small cell lung cancer) followed by either radiotherapy or cystectomy. However, some individuals may not be able to tolerate extensive chemotherapy, yet symptom control is necessary. In the case of our patient, his health status did not allow him to undergo extensive chemotherapy. Therefore, to manage his symptoms, we performed a TUR-BT. Unfortunately, he died due to a heart attack ten days after the TUR-BT procedure. Given this patient had a history of angina pectoris for six years without regular treatment, the reason of death may potentially be acute pulmonary embolism, acute cardiovascular or cerebrovascular diseases rather than post-operative complications. In summary, we observed that immunohistochemical

staining played an important role in the diagnosis of SCCB, especially in cases that were difficult to distinguish based on morphology alone.

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