The Expression of TTF-1 in Small Cell Carcinoma of Urinary Bladder

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Abstract

Small cell carcinoma (SMCC) of the urinary bladder is a rare tumor, accounting for less than 1% of all malignant neoplasms in the urinary bladder. Recently, thyroid transcription factor-1 (TTF-1), a putative marker for tumors originating from the lung and thyroid, was found to be expressed in SMCC of the urinary bladder, albeit in only a very small number of cases. Herein we report two additional cases of SMCC of the urinary bladder expressing TTF-1. The first patient was a 68-year-old white male with a 5-year history of a small focus of prostatic adenocarcinoma (biopsy proven) who was being treated with brachytherapy. He subsequently developed multiple large nodules at the base of the bladder, which by biopsy identified the presence of loosely cohesive small cells with minimal cytoplasm, coarsely and finely granular chromatin and indistinct nucleoli. Tumor cells were positive for TTF-1, CD56, chromogranin, synaptophysin and Cam 5.2, and negative for PSA. The location, morphological and immunochemical features of the tumor were diagnostic for SMCC of the urinary bladder. The second patient was a 76-year-old white female with a history of recurrent episodes of urinary tract infections. A biopsy showed a poorly differentiated carcinoma. The subsequent cystectomy revealed the presence of a 4.5 x 4.5 x 2.1 cm. tumor composed of a mixture of infiltrating high grade urothelial carcinoma and small cell carcinoma. The small cell component possessed similar morphological and immunohistochemical features as previously described in the first case, including positive expression for TTF-1. These two cases illustrate and concur with previous assertions that TTF-1 cannot be used to distinguish primary SMCC of the urinary bladder from metastatic SMCC of lung. *[N A J Med Sci. 2009;2(3):94-96.]*

Introduction

Small cell carcinoma (SMCC) is a group of highly aggressive tumors characterized by a distinctive morphology and a neuroendocrine phenotype. The majority of SMCCs originate in the lung; however, it has been described in many extrapulmonary locations, including pancreas, gastrointestinal tract, oropharyngeal mucosa, breast, uterine cervix, prostate, and urinary bladder.[1] SMCC of the urinary bladder is a rare tumor accounting for 0.5% to 1.0% of all urinary bladder malignancies. It can be the single component of the tumor, but more often it is associated with other carcinoma elements such as urothelial carcinoma, adenocarcinoma, sarcomatoid urothelial carcinoma, or mixtures of these components.[2,3] Similar to its pulmonary counterpart, SMCC of the urinary bladder is very aggressive and rapidly develops metastases. It has a mean survival in months and 5 year survival rate of about 8%.[4] The prognosis for SMCC is generally poor and has been shown to be partially dependent on the primary disease site.[8] Therefore, it is important to have an accurate diagnosis and establish the site of origin of a SMCC so that the appropriate course of medical treatment can be pursued. Unfortunately, irrespective of the site of origin, these tumors have nearly identical histopathologic features which make the identification of the primary tumor site almost impossible if site of origin is based solely on morphology. Under this condition, immunohistochemistry may be valuable in the evaluation of these lesions.

Thyroid transcription factor-1 (TTF-1), a nuclear homeodomain transcription factor, has been found to be expressed in a number of histological types of thyroid and lung carcinoma. It has been shown to be a useful marker in determining whether an adenocarcinoma of unknown primary is of pulmonary origin,[5,15] and in distinguishing pulmonary adenocarcinoma from mesothelioma.[16] TTF-1 expression in primary lung SMCC is 83% to 100% [5] while it also has been found to be expressed in some extrapulmonary SMCC.[6] Its value in distinguishing pulmonary from extrapulmonary SMCC is controversial. Previously, the expression of TTF-1 in SMCC of the urinary bladder has been demonstrated although in only a very small number of cases.[6,7] Here we report two cases of SMCC of urinary bladder expressing TTF-1.

Case Report

The first patient was a 68-year-old white male with a past history of prostatic cancer (adenocarcinoma) which was unresectable due to severe and extensive induration and scaring of the soft tissue around the prostate. He was treated with brachytherapy and hormone therapy. Five years later, he presented with decreased urine output with increased creatinine levels. A diagnosis of acute renal failure secondary

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to obstructive uropathy was made. A cystoscopy showed multiple large nodules presented at the base of the bladder which distorted the entire anatomy of the bladder base and blocked the ureteral orifices. A biopsy of the nodules showed loosely cohesive sheets and nests of small to intermediate sized cells with minimal cytoplasm, hyperchromatic nuclei, coarsely and finely granular chromatin, indistinct nucleoli, common mitotic activity and necrosis (**Figure 1A**). Tumor cells were positive for Cam 5.2, CD56, neuron-specific enolase, synaptophysin, chromogranin and TTF-1 and negative for CK 7, CK 20 and PSA (**Figure 1C, 1E** and data not shown). The morphology along with the immunohistochemical profile of the tumor is diagnostic for small cell carcinoma of the urinary bladder.

The second patient was a 76-year-old white female with a history of recurrent episodes of urine tract infections and urinary retention for three months. A cystoscopy showed a necrotic patch in the posterior wall of the bladder and the pathological diagnosis for the biopsy from this lesion was poorly differentiated carcinoma with necrosis. The subsequent cystectomy revealed the presence of a 4.5 x 4.5 x 2.1 cm. tumor composed of a mixture of infiltrating high grade urothelial carcinoma and small cell carcinoma. The small cell component possessed similar morphological and immunohistochemical features as previously described in the first case, including focally positive for TTF-1 (Figure 1 B, D, F and data not shown).

Discussion

SMCC of the urinary bladder is an uncommon tumor in the bladder with generally poor prognosis. Different hypotheses have been proposed for the etiological factors of SMCC of urinary bladder.[9,10] Among them, the most widely accepted one is that SMCC arises from multipotent stem cells of the urinary bladder, which may explain not only the coexistence of mixed malignancies with SMCC but also the heterogeneity of the immunohistochemical-staining pattern within SMCC. Previous studies have shown that SMCC of the urinary bladder frequently expresses epithelial markers such as the epithelial membrane antigen, AE1/AE3, and Cam 5.2 and neuroendocrine markers including neuron-specific enolase (NSE), chromogranin, synaptophysin.[11,12] Although nonspecific, NSE was the most sensitive and most frequently expressed neuroendocrine marker (90%).[13] Chromogranin A was positive in half of the cases with SMCC but only 5% of urothelial carcinoma. Cytokeratin 20 (CK20) was positive in 46–73% of urothelial tumors and was negative in SMCC tumors.[14] Consistent with these studies, we found in our cases that tumor cells were positive for Cam 5.2 and the neuroendocrine markers (synaptophysin, chromogranin and CD56). The additional finding of negative expression for CK20 supports the diagnosis of SMCC. In the first case, the patient had a past history of prostatic adenocarcinoma which was less than 5% of the total volume of all core biopsies. The stain of tumor cells for PSA in this patient's urinary biopsy was negative. The history, morphology and immunohistochemical profile of the urinary bladder lesion rule out the possibility of its being a metastatic prostatic adenocarcinoma.

Several studies have been performed comparing the expression of TTF-1 in pulmonary SMCC and extrapulmonary SMCC to evaluate the use of TTF-1 in distinguishing these two entities. The conclusions of these studies are controversial. Ordonez et al found TTF-1 expression in 27 of 28 (96%) pulmonary SMCCs and in only 4 of 54 (7%) extrapulmonary SMCCs and concluded that, although not a specific marker for SMCC of the lung, TTF-1 may be of use in distinguishing pulmonary SMCC from extrapulmonary SMCC.[16] However, Cheuk et al found TTF-1 expression in 43 of 52 (83%) pulmonary SMCCs and in 21 of 50 (42%) extrapulmonary SMCCs.[6] Agoff et al also found that 44% of nonpulmonary SMCCs were TTF-1 positive.[7] The results of these studies demonstrate that TTF-1 expression is not limited to SMCCs of the lung but may be present in SMCCs of various primary sites. The high frequency of expression of TTF-1 in extrapulmonary SMCCs strongly disputes the use of this marker to distinguish primary from metastatic SMCCs.

The expression of TTF-1 in SMCC of urinary bladder has been demonstrated by several studies. Cheuk et al[6] and Agoff et al [7] reported TTF-1 expression in 1 of 3 and 2 of 4 cases of SMCC of the urinary bladder, respectively. In two other larger studies, Jones et al[17] demonstrated TTF-1 expression in 17 of 44 (39%) cases of SMCC of urinary bladder and Alijo et al[18] found TTF-1 expression in 12 of 44 (27%) cases of SMCC of urinary bladder. There was no correlation between TTF-1 expression and pathological T stage, lymph node metastasis, or distant metastasis. In addition, TTF-1 immunoreactivity showed no correlation with any of the clinical parameters analyzed in these studies, including age, sex, smoking history, or clinical stage. We report two more TTF-1 positive SMCC of urinary bladder cases. One important differential diagnosis for SMCC of urinary bladder is metastatic SMCC from the lung. Although rare, metastasis to this site has been reported in association with widely disseminated disease.[19] The finding of TTF-1 expression in SMCC of urinary bladder makes it inappropriate to be used to distinguish primary SMCC of urinary bladder from metastatic SMCC of the lung. On the other hand, the urinary bladder must be considered as a possible site of origin in cases of TTF-1–positive metastatic SMCC of unknown primary.

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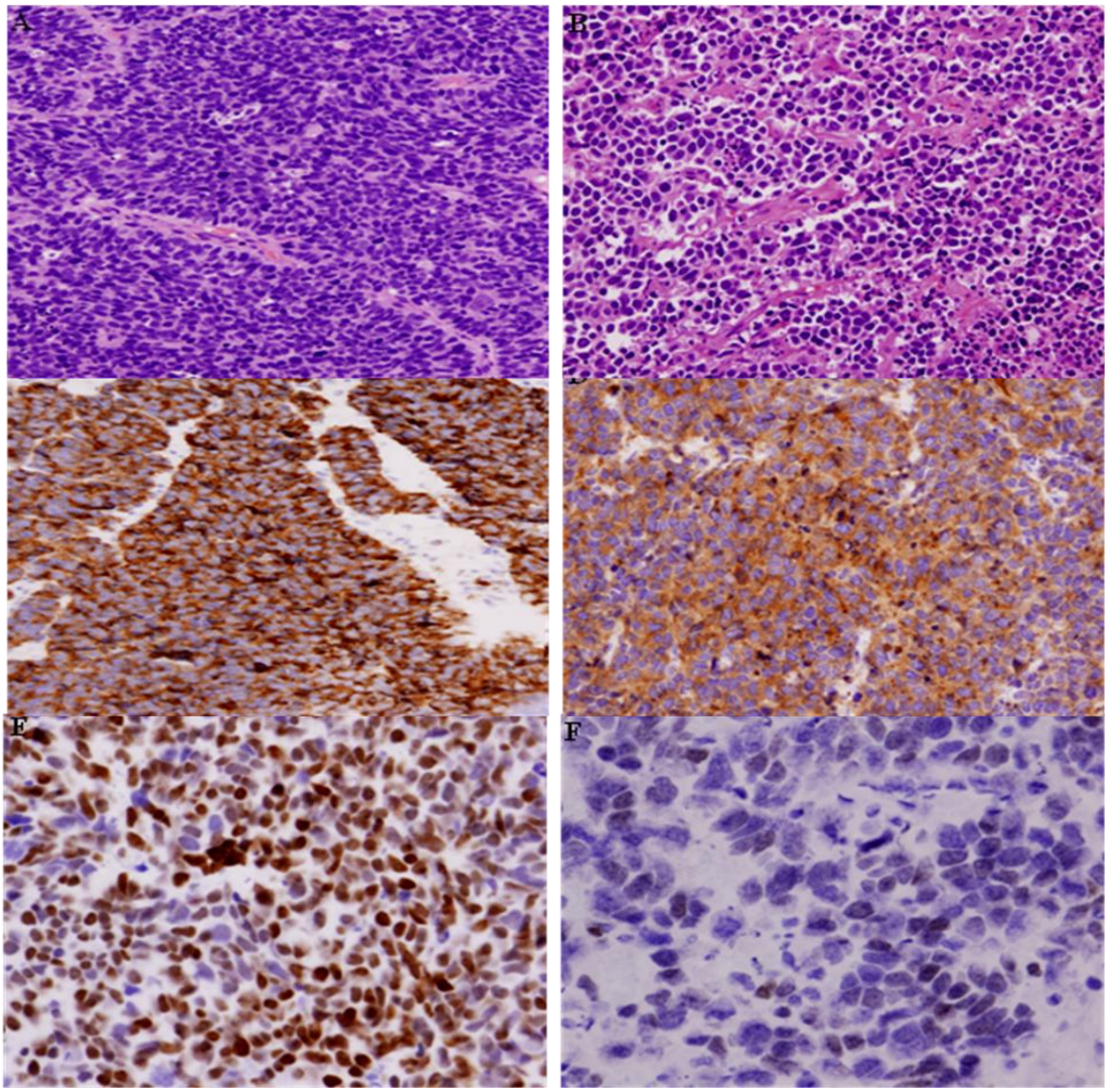

Figure 1. Hematoxylin-Eosin staining and immunostaining for synaptophysin and TTF-1 in SMCC of urinary bladder.
A and B: Hematoxylin-Eosin staining of tumor cells from case 1 (A) and case 2 (B), low power.
C and D: Synaptophysin staining of tumor cells from case 1 (C) and case 2 (D), low power**.**
E and F: TTF-1 staining of tumor cells from case 1 (E) and case 2 (F), high power.