



Thyroid transcription factor 1 expression in small cell carcinoma of the urinary bladder: an immunohistochemical profile of 44 cases

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Summary Small cell carcinoma of the urinary bladder is a rare and aggressive tumor resembling small cell carcinoma of the lung. Thyroid transcription factor 1 (TTF-1) expression is common in small cell carcinomas arising in the lung. However, studies of its expression in extrapulmonary small cell carcinomas have yielded varying results. Because information concerning the immunohistochemical profile of small cell carcinoma of the urinary bladder is limited, we investigated the immunoreactivity of this tumor to a battery of antibodies in a series of 44 cases. Using 5- μ m sections cut from paraffin-embedded tissue blocks, immunohistochemistry was performed to detect TTF-1, cytokeratin (CK) 7, CK20, and uroplakin antigenicity in 44 cases of small cell carcinoma of the urinary bladder. None of the patients had primary lung tumors. The TTF-1 immunohistochemical stain showed nuclear positivity in 17 cases (39%). Positive immunostaining for CK7 was observed in 26 cases (59%). There was no positive staining with either CK20 or uroplakin. There was no correlation between TTF-1 expression and survival ($P = .27$). In addition, TTF-1 expression did not correlate with clinicopathological characteristics, including age ($P = .74$), sex ($P = .53$), smoking history ($P = .96$), clinical stage ($P = .10$), pathological T stage ($P = .50$), lymph node metastasis ($P = .40$), and distant metastasis ($P = .58$). In summary, TTF-1 expression in small cell carcinoma of the urinary bladder was found in 39% of the tumors, demonstrating that this marker is expressed in small cell carcinomas other than those of pulmonary origin. Small cell carcinoma of the urinary bladder is positive for CK7 immunostaining in 59% of cases consistent with its origin from urothelium. Unlike urothelial carcinoma, expression of

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CK20 and uroplakin in small cell carcinoma of the urinary bladder is consistently negative, and thus, these stains do not appear to be useful in the diagnosis of this neoplasm. TTF-1 positivity is not a significant prognostic factor in small cell carcinoma of the urinary bladder.

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1. Introduction

Small cell carcinoma of the urinary bladder is an uncommon tumor accounting for less than 1% of all urinary bladder carcinomas [1,2]. Small cell carcinoma of the urinary bladder behaves aggressively, similar to its pulmonary counterpart [1,3-5]. This neoplasm is associated with tobacco smoking and is frequently seen in association with other carcinoma components, such as urothelial carcinoma, adenocarcinoma, sarcomatoid urothelial carcinoma, or mixtures of these components [5,6].

Because of the uncommon occurrence of small cell carcinoma of the urinary bladder, information concerning its immunohistochemical profile is limited. Thyroid transcription factor 1 (TTF-1) has been shown to be expressed in small cell carcinomas of the lung and, in one study, has been proposed as a marker useful in distinguishing small cell lung cancers from extrapulmonary small cell carcinomas [7]. However, this is controversial, and other studies refute this claim, documenting that a large number of extrapulmonary small cell carcinomas express TTF-1 [8]. Therefore, we examined the immunohistochemical staining pattern of this neoplasm using antibodies to TTF-1. In addition, antibodies for cytokeratin (CK) 7, CK20, and uroplakin were used to further elucidate the immunohistochemical profile of this tumor.

2. Materials and methods

2.1. Patients

Forty-four patients with small cell carcinoma of the urinary bladder were analyzed, including 34 men and 10 women. The patients' ages ranged from 36 to 83 years (mean, 66 years). All patients had advanced disease (T2 or above) at presentation. The pathological stages were T2 (21 patients), T3 (19 patients), and T4 (4 patients). The 2002 TNM classification system was used for pathological staging. Archival materials from these 44 cases of small cell carcinoma of the urinary bladder (accessioned from 1990 to 2003) were retrieved from the surgical pathology files. These 44 cases were selected for evaluation because of the availability of sufficient tissue for immunohistochemical studies.

2.2. Light microscopy and immunohistochemistry

Five-micrometer-thick sections were cut from the paraffin blocks and stained with hematoxylin and eosin for light microscopy. Histological slides were reviewed, and the

tumors fulfilled the criteria established for small cell carcinoma according to the World Health Organization (WHO) classification system [9]. In some tumors, the diagnosis of small cell carcinoma was made solely on morphological grounds, even if neuroendocrine differentiation could not be demonstrated by immunohistochemistry or electron microscopy studies, a diagnostic process that is acceptable according to WHO criteria [9]. Additional sections were obtained for immunohistochemical studies, which were performed on an automatic immunostainer. All cases were analyzed with antibodies against TTF-1, CK7, CK20, and uroplakin. All of the immunohistochemical stains and interpretations were performed at a single institution (Indiana University, Indianapolis, Ind).

Immunohistochemical stains for TTF-1 were carried out using monoclonal mouse anti-TTF-1 antibody (clone 8G7G3/1, 1:100 dilution; DAKO Corp, Carpinteria, Calif). CK7 and CK20 stains were performed using monoclonal mouse antihuman CK7 antibody (clone OV-TL 12/30, prediluted; DAKO Corp) and monoclonal mouse antihuman CK20 antibody (clone K_s20.8, prediluted; DAKO Corp). Uroplakin immunohistochemistry was accomplished using a mouse monoclonal immunoglobulin (clone AU1, prediluted; Research Diagnostics, Inc, Flanders, NJ). For the TTF-1, CK20, and uroplakin immunostains, all sections were subjected to heat-induced epitope retrieval using DAKO Target Retrieval Solution (DAKO Corp) for 20 minutes at 95°C. CK7 immunostaining used the avidin-biotin technique after proteinase K digestion for 5 minutes.

Nuclear staining of any tumor cells was considered a positive result. The percentage of cells staining positively for TTF-1, CK7, CK20, and uroplakin was estimated. The staining intensity was classified as negative (0), weak (1+), moderate (2+), or strong (3+), as previously described [10].

2.3. Statistical analysis

All statistical tests were 2-sided, with a *P* value of .05 or less considered to be statistically significant. SAS version 8.2 (SAS Institute, Cary, NC) was used for the statistical analysis. Kaplan-Meier survival curves were generated, and Cox proportional hazards models were fitted for time to death or lost to follow-up. Fisher exact test for differences in frequencies was used for analyzing the TTF-1 expression and survival and other clinicopathological parameters.

3. Results

All tumors were classified according to criteria established by the WHO classification system [9], which are

identical to the criteria for small cell carcinoma of the lung. The carcinomas were composed of sheets of small cells separated by delicate fibrovascular stroma. The cells had uniformly small, round-to-oval, overlapping nuclei with evenly distributed chromatin and without prominent nucleoli. The cytoplasm was sparse. Mitotic figures were frequent in all tumors. Twenty-four of the 44 cases of small cell carcinoma had a concomitant urothelial carcinoma component.

Among the 44 cases of small cell carcinoma of the urinary bladder, 17 (39%) showed positive immunohistochemical staining for TTF-1. In all positive cases, the staining pattern was nuclear (Fig. 1), in keeping with the fact that TTF-1 is a transcription factor. Two cases showed strong (3+) staining intensity; 8 cases showed moderate (2+) staining intensity; and 7 cases showed weak (1+) staining intensity. The percentage of positive staining cells ranged from 40% to 95%. None of the urothelial carcinoma components showed positive TTF-1 staining. CK7 positivity was seen in 26 cases (59%). Nine cases showed strong (3+) staining intensity; 11 cases showed moderate (2+) staining intensity; and 6 cases showed weak (2+) staining intensity. The percentage of cells staining positively for CK7 ranged from 8% to 99%. Immunohistochemical stains for CK20 and uroplakin were completely negative in all small cell carcinomas examined; however, positive expression of CK20 was seen in 12 of 24 urothelial carcinoma components.

During a median follow-up of 11 months (range, 1-113 months), 30 patients died of cancer; 2- and 5-year cancer-specific survivals were 38% and 9%, respectively. There was no correlation between TTF-1 expression and survival

($P = .27$). For TTF-1-positive tumors, 2- and 5-year cancer-specific survivals were 37% and 12%, respectively. For TTF-1-negative tumors, 2- and 5-year cancer-specific survivals were 38% and 7%, respectively. There was no correlation of TTF expression with other clinicopathological characteristics including age ($P = .74$), sex ($P = .53$), history of smoking ($P = .96$), clinical stage ($P = .10$), pathological T stage ($P = .50$), lymph node metastasis ($P = .40$), and distant metastasis ($P = .58$).

4. Discussion

Small cell carcinoma has been described at a number of anatomic sites. It is seen most frequently in the lung; however, it has been described in many extrapulmonary locations, including the skin, gastrointestinal tract, oropharyngeal mucosa, prostate, uterine cervix, breast, pancreas, and urinary bladder. The prognosis for small cell carcinoma is generally poor, with local therapy usually being insufficient for cure [1,3-5]. The prognosis has been shown to be partially dependent on the primary disease site [11]. A recent clinicopathological study of 64 cases of small cell carcinoma of the urinary bladder demonstrated a poor prognosis for this lesion with 68% of patients dying from their bladder carcinoma (mean follow-up of 21 months) and with no significant survival differences between patients who did and did not undergo cystectomy [5]. Consequently, a diagnosis of small cell carcinoma of the urinary bladder has important prognostic and therapeutic implications.

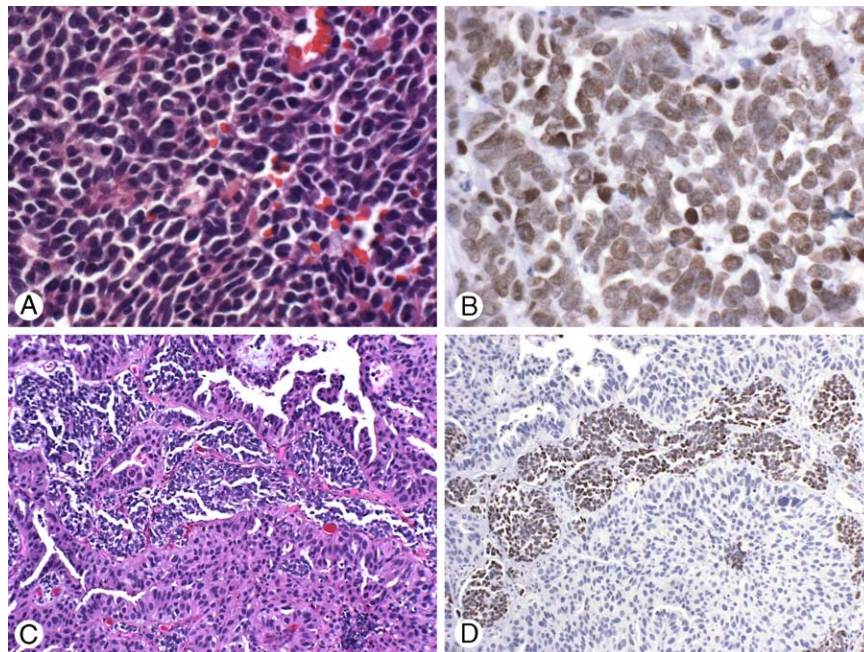


Fig. 1 TTF-1 immunohistochemistry. (A, B) TTF-1 immunostaining highlights the nuclei of the cancer cells in small cell carcinoma of the urinary bladder. (C, D) The small cell carcinoma component is distinguished from the urothelial carcinoma component by positive nuclear TTF-1 staining.

Because of the uncommon occurrence of this tumor, its immunohistochemical profile has not been previously well defined. Previous studies have shown that small cell carcinoma of the urinary bladder is frequently immunoreactive to antibodies against epithelial markers (epithelial membrane antigen, CK AE1/AE3, and CK Cam 5.2) and neuroendocrine markers (neuron-specific enolase, chromogranin, synaptophysin, Leu 7, serotonin, and vasoactive intestinal peptide) [1,2,4]. Although Cheuk et al [8] and Agoff et al [12] demonstrated TTF-1 expression in 1 of 3 cases and in 2 of 4 cases of small cell carcinoma of the urinary bladder, respectively, the immunohistochemical expression of TTF-1 in this tumor has not been studied in a large series of cases.

TTF-1 is a 38-kd homeodomain-containing transcription factor that is expressed in the thyroid, in the lung (type II pneumocytes and Clara cells), and in certain areas of the brain [13,14]. TTF-1 expression has been demonstrated in a number of histological types of thyroid and lung carcinomas by immunohistochemistry, including 83% to 100% of primary lung small cell carcinomas [13,15]. TTF-1 has been shown to be a useful marker in determining that an adenocarcinoma of unknown primary is of pulmonary origin [13,15], in distinguishing pulmonary adenocarcinoma from mesothelioma [7], and in distinguishing between pulmonary small cell carcinoma and Merkel cell carcinoma [16]. The use of TTF-1 in distinguishing pulmonary from extrapulmonary small cell carcinoma, however, is controversial. Ordoñez [7] found TTF-1 expression in 27 of 28 pulmonary small cell carcinomas and in only 4 of 54 extrapulmonary small cell carcinomas and concluded that, although not a specific marker for small cell carcinoma of the lung, TTF-1 may be of use in distinguishing small cell lung carcinoma from extrapulmonary small cell carcinomas. Different results were obtained by Cheuk et al [8] in a study of 102 cases of small cell carcinoma, who found TTF-1 expression in 43 (83%) of 52 pulmonary small cell carcinomas and in 21 (42%) of 50 extrapulmonary small cell carcinomas. Our finding of TTF-1 positivity in 17 (39%) of 44 cases of small cell carcinoma of the urinary bladder is more in keeping with the findings of Cheuk et al than with those of Ordoñez.

Our results confirm that TTF-1 expression is not restricted to small cell carcinomas of pulmonary origin. Indeed, 24 of the 44 cases of small cell carcinoma in the current study had a concomitant urothelial carcinoma component, confirming that these tumors are primary neoplasms of the urinary bladder. In all cases, the non-small-cell components were negative for TTF-1. Because immunohistochemical expression of TTF-1 is seen in 39% of cases of small cell carcinoma of the urinary bladder, the bladder must theoretically be considered as a potential site of origin in TTF-1-positive metastatic small cell carcinomas of unknown primary; however, bladder cancer rarely presents as an occult primary tumor. The majority of patients with small cell carcinoma of the urinary bladder

present at a high clinical stage with symptoms referable to the bladder, most commonly macroscopic hematuria [5].

TTF-1 immunoreactivity has been studied as a prognostic factor in non-small-cell lung carcinomas [17-20]. In multivariate analysis, positive TTF-1 staining was associated with a better patient outcome ($P = .05$) [17]. Patients with tumors expressing TTF-1 had a median survival of greater than 57.3 months compared with 39.4 months for patients with TTF-1-negative tumors ($P = .0067$) [17]. Loss of TTF-1 expression in non-small-cell carcinomas was associated with aggressive behavior. In addition, TTF-1 expression has shown an inverse correlation with Ki-67 proliferative activity in non-small-cell lung carcinomas, a finding that may imply a relatively good prognosis for patients with this tumor type [19]. The association between TTF-1 positivity and prognosis in small cell carcinomas of pulmonary and extrapulmonary origin has not been extensively studied. Whereas TTF-1 immunohistochemistry is of potential use in the diagnostic arena, TTF-1 positivity in small cell carcinoma of the urinary bladder does not appear to be of any prognostic significance. Differences in 2- and 5-year cancer-specific survival between patients with and without TTF-1-positive tumors were not significant. There was also 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, including age, sex, smoking history, or clinical stage.

In addition to studying the expression of TTF-1 in small cell carcinoma of the urinary bladder, we also examined the expression of CK7, CK20, and uroplakin in this tumor. CK7 expression was seen in 59% of the cases examined, which is consistent with the findings in previous studies of the immunoprofile of this neoplasm [1,2,4]. It is also consistent with the frequent finding of CK7 positivity in urothelial carcinoma [21] with which small cell carcinoma is frequently associated and from which small cell carcinoma in the bladder has been postulated to arise [6]. CK20 has been shown to be frequently expressed in some neuroendocrine tumors, such as Merkel cell carcinoma. We found no CK20 immunoreactivity in any of the 44 cases of small cell carcinoma of the urinary bladder. This finding is consistent with prior studies showing the frequent absence of CK20 expression in small cell carcinomas of both pulmonary and extrapulmonary origin [7,8]. The lack of expression of CK20 in small cell bladder carcinomas is an interesting finding because CK20 expression has been frequently documented in normal urothelium, urothelial dysplasia, and urothelial carcinoma and because CK20 expression has been proposed as a marker for malignant behavior in urothelial carcinoma [22]. CK20 dysregulation with increased expression of this marker has been associated with the development of urothelial dysplasia and carcinoma [23-26]. In our 24 cases of small cell carcinoma with a coexisting urothelial carcinoma component, 12 cases

(50%) showed positive CK20 staining in the urothelial carcinoma. This percentage of CK20 positivity in urothelial carcinoma is similar to previously reported rates of 46% to 73% [27,28].

Uroplakin is a transmembrane protein expressed by urothelial lining cells, which has been shown to be a specific and moderately sensitive immunohistochemical marker of urothelial lesions [29-31]. We found no immunohistochemical evidence of uroplakin expression in any of the 44 cases of small cell carcinoma of the urinary bladder in this study. A loss of uroplakin expression during the progression from noninvasive to invasive urothelial carcinoma has been proposed [29] and may be one factor explaining the complete lack of immunoreactivity observed in this study. Based on our findings, uroplakin appears to be of little value in assessing the differential diagnosis of a small cell carcinoma of indeterminate origin.

In summary, small cell carcinoma of the urinary bladder is an uncommon neoplasm for which the immunohistochemical profile includes a variety of epithelial and neuroendocrine markers. We found TTF-1 expression in 39% of cases, which is in accordance with prior studies demonstrating TTF-1 positivity in extrapulmonary small cell carcinomas. Thus, the urinary bladder must be considered as a possible site of origin in cases of TTF-1-positive metastatic small cell carcinoma of unknown primary. TTF-1 positivity is not a significant prognostic factor in small cell carcinoma of the urinary bladder. We found CK7 positivity in 59% of cases, consistent with this tumor's known expression of a variety of epithelial markers. Negative immunostaining for CK20 was seen in all 44 cases of small cell carcinoma of the urinary bladder, a finding that is in striking contrast to the CK20 positivity typically observed in urothelial carcinoma. Uroplakin does not appear to be a useful marker for small cell carcinoma of the urinary bladder.

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