Small Cell Carcinoma of the Urinary Bladder
A Rare, Aggressive Neuroendocrine Malignancy

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Small cell carcinoma of the urinary bladder is a rare, often fatal, disease. Its presenting symptoms and gross morphology are similar to those of conventional urothelial carcinoma, whereas its prognosis is much poorer with frequent metastasis. Small cell carcinoma of the urinary bladder shares similar histology with its counterparts in other organs; however, its immunoreactivity to conventional neuroendocrine markers is low. Its diagnosis is thus considered permissible on morphologic grounds alone. Multimodal treatments are often employed, although no definite treatment algorithm has been established. For this extremely aggressive malignancy with an as-yet inconclusive etiology, further studies are needed to clarify its molecular pathogenesis to serve as a basis for diagnostic markers and therapeutic targets. The clinical, morphologic, immunoreactive, molecular, and therapeutic features of bladder small cell carcinoma are reviewed, including a detailed discussion on the utility of immunohistochemical markers.


Small cell carcinoma (SmCC) most commonly arises in the lower respiratory tract of chronic smokers and is usually rapidly evolving and lethal. It is not uncommon, however, for SmCC to arise in nonpulmonary sites. Histologic criteria for the diagnosis of extrapulmonary SmCC are the same as those for pulmonary SmCC: the appearance of uniform small cells with scant cytoplasm, powdery chromatin, and inconspicuous nucleoli. Despite their shared histologic morphologies, the clinical behaviors of SmCCs vary according to their anatomic sites.

Extrapulmonary SmCC has been reported to arise in almost all body sites except the central nervous system. Primary sites include esophagus, gastrointestinal tract, pancreaticobiliary system, larynx, salivary glands, uterus, cervix uteri, vagina, urinary bladder (Figure 1, A through D), prostate, breast, and lacrimal gland. Merkel cell carcinoma of the skin shares certain histomorphologic features with SmCC.

The SmCCs, both pulmonary and extrapulmonary entities, may share the same origin. They may derive from cells of the amine precursor uptake and decarboxylation system, which originate in neural crest and then migrate to different epithelial sites within the body. These amine precursor uptake and decarboxylation cells are characterized by the presence of intracytoplasmic neurosecretory granules and may stain positive with chromogranin A (CGA). Another postulated cellular origin of SmCCs is from a multipotent stem cell with the ability to differentiate into various tissue types. Some clonality studies have indicated that bladder SmCC may share a common origin with urothelial carcinoma (UC; also referred to as transitional cell carcinoma) of the urinary bladder because they share many common molecular abnormalities, as discussed in detail below.

Epidemiology

In 2011, there will be 69,250 estimated new cases and 14,990 deaths from bladder cancer in the United States.1 Bladder cancer, as a whole, is 3 times more common in men than it is in women. In men, bladder cancer is the fourth most common malignancy after prostate, lung, and colorectal cancers. In women, it is the ninth most common malignancy. More than 90% of bladder cancers are UCs. For the nonurothelial epithelial malignancies of the urinary bladder, the 2 most common entities are squamous cell carcinoma and adenocarcinoma. Neuroendocrine tumors are much less frequent and are classified into 2 subcategories: carcinoid tumor and neuroendocrine carcinoma. Neuroendocrine carcinoma is further subdivided into SmCC and large cell neuroendocrine carcinoma, the latter of which is vanishingly rare in the urinary bladder.2

The SmCC of the urinary bladder accounts for only 0.3% to 0.7% of all primary bladder cancers. The first case was reported in 1981.3 Since then, approximately 400 cases, including several large series, have been reported in the medical literature. Bladder SmCC most commonly presents in the seventh decade, with a mean age of presentation at approximately 67 years.4 Existing cases show a striking male predisposition, with a male to female ratio of up to 5:1. The largest case series to date has followed 64 patients from multiple hospitals around the world and has confirmed an advanced stage at diagnosis and a survival of only a few months after diagnosis.5 Cigarette smoking is an accepted

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risk factor for bladder SmCC, with 50% to 70% of patients reporting a smoking history. Significant second-hand smoking or chemical exposure may also be contributory. In addition, many patients with bladder SmCC have common, nonspecific risk factors, including bladder calculi, bladder manipulation, and chronic cystitis.

**CLINICAL FEATURES**

The age, gender predilection, and symptoms at presentation of bladder SmCC are similar to those of bladder UC. As with bladder UC, patients with bladder SmCC can present with dysuria, obstructive voiding symptoms, weight loss, abdominal pain, and/or recurrent urinary tract infections. In both SmCC and UC of the urinary bladder, the most common presentation is painless gross hematuria (67%–100% in bladder SmCC), with or without dysuria. Bladder SmCC is infrequently associated with paraneoplastic syndromes, in contrast to its pulmonary counterpart. The uncommonly presented paraneoplastic syndromes include hypercalcemia, Cushing syndrome, and sensory neuropathy.

The biologic behavior of bladder SmCC, on the other hand, is much more aggressive when compared with stage-matched bladder UC. Bladder SmCC is associated with a high frequency of distant metastases and poor survival. Median survival is around 20 months. Most patients (94%) with bladder SmCC present with muscle invasion, and approximately 67% of patients develop systemic metastases during the disease course. Metastasis commonly involves liver (Figure 2, A and B), brain (Figure 2, C and D), lung, bone, lymph node, and less frequently, adrenal gland, pancreas, and spleen, among other sites. As compared with bladder UC, bladder SmCC also often presents at a later stage. Bladder SmCC presents as stage I in 0% to 5% of patients, stage II in 27% to 44% of patients, stage III in 24% to 30% of patients, and stage IV in 27% to 43% of patients.

Prognosis is dependent on performance status and the extent of disease at diagnosis, whereas overexpression of p53, patient age, sex, and presenting symptoms do not appear to correlate with prognosis. Histologically, pure SmCC tends to have a poorer outcome than mixed SmCC.
of the urinary bladder. Prognosis does not seem to be significantly affected by therapy, and patients undergoing cystectomy die of disease after a similar median time as patients who do not have surgery.

**MORPHOPATHOLOGY**

Grossly, SmCC of the urinary bladder most commonly presents as a solid polypoid mass (Figure 1, A). At cystoscopy, bladder SmCC usually cannot be distinguished from bladder UC by its gross appearance. Exfoliative urine cytology may or may not reveal the lesional cells (Figure 1, B). Accurate diagnosis is achieved by histomorphologic examination of the tissue sampled via transurethral resection.

Microscopically, bladder SmCC is identical to SmCC of the lung or the other sites; for this reason, a neuroendocrine cell origin is generally favored. The tumor usually has a patternless type of diffuse growth, whereas occasionally and focally, nests and trabeculae are observed. The tumor cells have sparse cytoplasm and consequently exhibit nuclear crowding and molding. Nucleoli are often inconspicuous, and the chromatin is finely stippled (referred to as powdery or salt-and-pepper). Frequent mitoses, crush artifact, geographic necrosis, and Azzopardi effect are indicative of its high proliferation rate (Figure 1, C and D).

Compared with its pulmonary counterpart, which usually exhibits pure small cell growth, bladder SmCC is more frequently admixed with another histologic subtype, in approximately 40% to 50% of the cases. The mixed epithelial component is most commonly conventional UC, including carcinoma in situ, followed by squamous cell carcinoma and adenocarcinoma and, rarely, even sarcomatoid (spindle cell) carcinoma. The frequent association of bladder SmCC with otherwise conventional UC has led to a proposed common origin for both tumors, suggesting that small cell appearance may represent dedifferentiation within urothelial cell neoplasms. Mixed tumors, even with only focal small cell histology, show dismal prognosis that is more similar to that of pure SmCC than to UC or pure tumors consisting of other components, warranting, therefore, a diagnosis as SmCC.

**IMMUNOPHENOTYPING: IMPORTANCE IN DIAGNOSIS AND UTILITY OF NOVEL MARKERS**

Histomorphologically, bladder SmCC resembles its counterparts elsewhere in the body (Figure 1, C and D). Unlike SmCC of most other organs, however, the sensitivity of conventional neuroendocrine markers, such as, synaptophysin, CGA, neuron-specific enolase (NSE), CD56, and the like, has been relatively low in bladder SmCC cases. Therefore, the World Health Organization diagnostic criteria allow for the diagnosis of bladder SmCC to be made on morphologic grounds alone. The quest for sensitive and specific immunohistochemical markers for bladder SmCC remains of interest. The following subsections present detailed discussions on each of these markers of relevance.
Neuroendocrine Markers

As mentioned above, the diagnosis of bladder SmCC can be made solely on morphologic grounds, with the help of immunohistochemistry to document neuroendocrine differentiation. However, conventional neuroendocrine markers generally have low sensitivity for bladder SmCC.

Chromogranin A (CGA, also referred to as parathyroid secretory protein 1, encoded by gene CHGA) is a member of the granin (chromogranin and secretogranin) family of neuroendocrine secretory proteins, a family of regulated secretory proteins ubiquitously found in the cores of amine/peptide hormone and neurotransmitter dense-core secretory vesicles. Because of its association with amine/peptide secretory materials, CGA is expressed in chromaffin cells (adrenal medulla, paranganglia, among others), enterochromaffin-like cells, and β cells of the pancreas but not in steroid hormone producing cells (adrenal cortex, gonads, for instance). In the case of bladder SmCC, CGA is the least sensitive of the neuroendocrine markers, staining one-third to one-half of the bladder SmCC cases (Figure 3, A). In comparison, it is positive in only 5% of bladder UC cases.

Synaptophysin (also referred to as major synaptic vesicle protein p38, encoded by gene SYT) is a synaptic vesicle glycoprotein with a molecular weight of 38 kDa. It is present in neuroendocrine cells, including both amine/peptide and steroid hormone producing cells, and in all neurons in the brain and spinal cord that participate in synaptic transmission. CD56 (also referred to as neural cell adhesion molecule, encoded by gene NCAM1) is a homophilic binding glycoprotein, physiologically expressed on the cell membrane of neurons, glia, skeletal muscle, and natural killer cells; it plays a role in cell-cell adhesion, synaptic plasticity, and neurite overgrowth. In the case of bladder SmCC, the sensitivity of synaptophysin (Figure 3, B) and CD56 is moderately higher than that of CGA. A recent study has reported that CD56 may be among the most sensitive neuroendocrine markers, staining 71.4% of bladder SmCC cases, followed by synaptophysin (64.3%) and CGA (28.6%).

The NSE marker (also referred to as γ-enolase or enolase 2, encoded by gene ENO2) is a phosphopyruvate hydratase, is 1 of the 3 enolase isoenzymes found in mammals. The NSE isoenzyme is expressed in mature neurons and cells of neuronal origin. In the case of bladder SmCC, it may be expressed in 80% of cases or more. The specificity of NSE, however, is very low.

Thyroid Transcription Factor 1

Thyroid transcription factor 1 (TTF-1; also referred to as NK2 homeobox 1, encoded by gene NKX2-1) is a 38-kDa homeodomain-containing transcription factor. It is expressed in the nuclei of thyroid follicular cells, certain lung cells (mainly Clara cells and type II pneumocytes), and cells in the diencephalon area of the brain. TTF-1 has been identified by immunohistochemistry in most SmCC and adenocarcinomas of the lung and in follicular cell-derived thyroid tumors. It was once proposed as a specific marker to determine the origin of metastasis from those tumor types. However, the once-alluded specificity of TTF-1 for lesions of pulmonary and thyroid origin has been increasingly questioned. A case series in 2001 found TTF-1 positivity in 42% (21 of 50) of extrapulmonary SmCC cases, including 2 bladder primaries. It was thus concluded that TTF-1 was not reliable for use in determining the primary site of SmCC. Nonetheless, TTF-1 is still useful for the differential diagnosis of extracutaneous SmCC metastasis to the skin versus primary Merkel cell carcinoma of the skin because most studies have confirmed that Merkel cell carcinoma is consistently negative for TTF-1.

Although expressed in a significant percentage of extrapulmonary SmCC and virtually all pulmonary SmCC, TTF-1 is positive in only 20% to 39% of bladder SmCC. In a reported series of 44 bladder SmCC cases, in 50% (22 of 44) of cases no TTF-1 positivity was found in the areas of conventional UC adjacent to SmCC. In bladder SmCC, as well as in 2 undifferentiated large cell carcinomas of the bladder, TTF-1 expression was found in only 25% of cases, whereas synaptophysin and NSE were positive in 50% and 80% of cases, respectively. Because bladder SmCC may express TTF-1 (Figure 3, C), the urinary bladder should be included as a possible primary source of metastatic SmCC expressing this marker. As for prognostic value, although TTF-1 expression has been demonstrated to be associated with a better prognosis in non–small cell carcinoma of the lung, no correlation has been found between TTF-1 expression and the prognosis of SmCC of the urinary bladder or other body sites.

p16

p16 (also referred to as cyclin-dependent kinase inhibitor 2A, encoded by gene CDKN2A) is a tumor suppressor protein. p16 plays an important role in cell cycle regulation. p16 mutations increase the risk of developing a variety of neoplasms, most notably melanoma. Other defects or alterations in the p16-retinoblastoma (Rb) pathway have been frequently observed in malignant neoplasms. Inactivation of the Rb gene by human papillomavirus viral oncoproteins has been considered an essential step in the pathogenesis of cervical neoplasia. Rb gene inactivation, and the resultant loss of function of the Rb protein, is accompanied by p16 overexpression because of the disruption of a negative feedback mechanism. In the lungs, more than 90% of patients with SmCCs have mutations in the Rb gene and demonstrate increased, intense p16 immunoreactivity.

Normal tissues, including normal urothelial mucosa (epithelial and stromal cells), exhibit a heterogeneous staining pattern, with p16 positivity in 1% to 10% of the nuclei and a certain degree of variation because of technical factors. In one study, where 5% of nuclei staining positive for p16 was used as the cutoff to determine p16 immunopositivity, positive p16 staining was found in the mucosa of 100% of normal bladder. In a more recent study, where a higher cutoff value was used because of the well-recognized level of p16 staining in normal bladder tissue, abnormal p16 expression was defined as positive p16 immunoreaction in more than 10% of tumor cell nuclei. In this latter study, all but one (92.8%) of bladder SmCC cases and 43.7% of high-grade bladder UC cases showed p16 overexpression, a significant difference between those two entities. This provides support for the hypothesis that alterations of the p16-Rb pathway may be an early and necessary event in the pathogenesis of bladder SmCC. On a more practical note, p16 may be particularly useful as a positive marker for bladder SmCC (Figure 3, D) in view of the often focal/minimal positivity for conventional neuroendocrine markers. Negativity for p16 should raise caution about a diagnosis of bladder SmCC.
Tumor protein p63 (TP63, also referred to as transformation-related protein 63, encoded by gene TP63) is a member of the p53 family of transcription factors, which also include p73 and the well-known p53. Although discovered much later than p53, based on molecular phylogenetic analysis, p63 is now considered the prototype from which p53 and p73 have evolved. p63 expression has not yet been extensively studied in bladder SmCC. For bladder UC, 2 tissue microarray studies have reported inverse correlation between p63 immuno-

Figure 3. Immunohistochemical profile of small cell carcinoma of the urinary bladder. Bladder small cell carcinoma cells may exhibit variable positivity for conventional neuroendocrine markers, including chromogranin A (A) and synaptophysin (B). Tumor cells may be diffusely positive, focally/weakly positive (C), or negative for TTF-1. p16 is positive in most bladder small cell carcinoma cases (D). p63, which is often positive in urothelial carcinoma (E) and CK20, which is often positive in urothelial carcinoma and Merkel cell carcinoma (F), in contrast, are usually negative in bladder small cell carcinoma (original magnifications ×400).
reactivity and tumor grade and stage. In one of those studies, positive p63 staining (expression in >10% of tumor cell nuclei) was demonstrated in 100% of pTa UC, whereas only 77% of pT2 UC stained with p63. No statistical correlation has been found between survival and p63 expression in patients with bladder UC. A recent study on bladder SmCC immunoprofiling has shown a significant difference in p63 immunoreactivity between SmCC and high-grade UC of the urinary bladder. Almost all bladder SmCC cases (92.8%) were negative for p63 (Figure 3, E), whereas p63 immunoreaction was positive (expression in >10% of tumor cell nuclei) in 81.3% of bladder high-grade UC cases, suggesting that p63 is a helpful immunohistochemical marker in differentiating bladder SmCC from bladder UC.13

Cytokeratins

The tumor cells of bladder SmCC frequently exhibit a dotlike positivity for pancytokeratin. Regarding individual cytokeratin markers, case series on bladder SmCC demonstrated CAM 5.2 reactivity in 67% (14 of 21), 34bE12 in 40% (4 of 10), and epithelial membrane antigen in 78% (14 of 18) of the cases studied. CK20, although negative in most SmCC (pulmonary and extrapulmonary, excluding Merkel cell carcinoma of the skin), highlights 46% to 73% of bladder UC cases. CK20 expression has been proposed to be associated with lower biologic aggressiveness of bladder UC. As mentioned, bladder SmCCs are typically negative for CK20 (Figure 3, F); however, approximately one-half of the bladder high-grade UC cases can also be negative for this marker.15 Low-grade UC, on the other hand, is nearly always positive for CK20.24 Similar immunoreactive nonspecificity has also been observed for CK7; CK7 not only stains positive in most cases of bladder UC but also marks more than one-half of bladder SmCCs. A recent case-control study demonstrated that most cases of bladder high-grade UC (81.3%) stained with CK7, whereas only 50% of bladder high-grade UC cases were positive for CK20. CK7 was positive in 64.3% of bladder SmCC cases, whereas only 2 of them exhibited focal staining with CK20.

Other Differential Diagnostic Markers

Uroplakin is a group of transmembrane proteins that are widely regarded as urothelium-specific markers of terminal urothelial cytodifferentiation. Urothelia at different anatomic sites differ in their embryonic origin and cellular differentiation, as reflected in their different uroplakin content. Subsequent to malignant transformation, the tight differentiation-restricted expression of uroplakin in normal urothelium may be lost. Therefore, this marker exhibits variable positivity in bladder UC cases. Given its high specificity to urothelia, not surprisingly, uroplakin was found to be negative in all 44 bladder SmCC cases examined in a case series.17

CD44v6 is a splice variant of CD44, a group of transmembrane glycoproteins expressed in a large variety of mammalian cell types, which mediates cell-cell and cell-matrix adhesion. CD44v6 confers metastatic potential and has been associated with aggressive behavior in certain malignancies. It was positive in 57% (12 of 21) of the cases of moderately or poorly differentiated bladder UC. In contrast, weak CD44v6 expression was found in only 6.8% (3 of 44) of bladder SmCC cases.25 It is important to distinguish bladder SmCC from its counterpart of the prostate, which is a relatively common source of extrapulmonary SmCC in men. Gene fusion between erythroblastoasis virus E26 transforming sequence (ETS) genes, particularly the ETS-related gene (ERG), and transmembrane protease serine 2 (TMPRSS2) has recently been identified in prostatic malignancies. TMPRSS2-ERG gene fusion was found in 47% (14 of 30) of prostatic SmCC, a frequency comparable to that of prostatic acinar adenocarcinoma. Of note, this gene fusion has been consistently absent in bladder SmCC cases. Actually, ERG rearrangements have not been identified in any nonprostatic carcinomas so far. Thus, in cases of prostatic SmCC, TMPRSS2-ERG gene fusion has a specificity approaching 100% and a sensitivity approximating at 50%. Therefore, the detection of a TMPRSS2-ERG gene fusion can be used to rule in a prostatic origin of SmCC, whereas its absence cannot be used to rule out prostatic origin or claim any nonprostatic origin. From a technical point of view, ERG immunohistochemistry is considered less optimal than fluorescence in situ hybridization for TMPRSS2-ERG gene fusion.26,27

Other Potential Therapeutic/Prognostic Markers

Tumor protein 53 (TP53, encoded by gene TP53) is a tumor suppressor protein crucial in multicellular organisms. It regulates the cell cycle and conserves genomic stability, thus its alias as “the guardian of the genome.” p53 gene mutation represents the most common genetic alteration in human neoplasias and has been associated with high grade, high stage, and poor prognosis in a variety of malignancies, including those of the lung, breast, stomach, prostate, and urinary bladder. The protein product of mutant p53 gene is significantly more stable than the wild type and subsequently accumulates in the cells, manifested as p53 overexpression on immunostaining. Multiple case series on bladder SmCC have documented p53 overexpression, ranging from 37.5% (3 of 8) to 80% (8 of 10) of the cases studied in individual series. The largest series to date demonstrated a p53 overexpression rate at 54% (27 of 50) of bladder SmCC cases. This case series revealed no definite correlation between p53 overexpression and poorer prognosis, possibly because the overall prognosis for bladder SmCC is poor, regardless of various clinicopathologic parameters.28

Proto-oncoprotein c-kit (also referred to as CD117, tyrosine protein kinase KIT, or mast/stem cell growth factor receptor, encoded by gene KIT) is involved in many physiologic and pathologic processes, including hematopoiesis and oncogenesis. Its sensitivity in bladder SmCC cases is rather low, demonstrated at 27% (14 of 52) and 28% (2 of 7) in 2 case series.29,30 Despite its limited value in establishing a diagnosis of bladder SmCC, c-kit may be a worthwhile therapeutic target in a subset of patients with this disease.

Human epidermal growth factor receptor 2 (Her2/neu, also referred to as ERBB2, CD340, or p185, encoded by gene ERBB2) is a member of the epidermal growth factor receptor family (ErbB protein family). It is overexpressed in a variety of carcinomas, including those of the breast, stomach, ovary, endometrium, lung, and urinary bladder. The Her2/Neu overexpression, when detectable by immunohistochemistry, is generally associated with a poor prognosis. Its typical membranous immunostaining was
observed in 50% (5 of 10) of bladder SmCC cases in one study. In brief summary, SmCC of the urinary bladder exhibits variable immunoreactivity to conventional neuroendocrine markers (synaptophysin, CGA, NSE, CD56, and the like) and relatively low positivity to TTF-1. Investigations on novel differential markers have suggested that p16 positivity and p63 negativity are characteristic of bladder SmCC, whereas p63 serves as the better first-line discriminator between bladder SmCC and bladder high-grade UC. The typical immunohistochemical profile of bladder SmCC is thus proposed to include p16+, p63-, and CK20-; in contrast, that of bladder high-grade UC is p16+, p63+, and CK20-. The recent observations of p53, c-kit, and Her2 expression in certain percentages of bladder SmCC cases may suggest new possibilities for the stratification of patients based on prognostic marker status and the application of immunotherapy. Further studies are warranted to better understand and apply those differential, therapeutic, or prognostic markers.

**MOLECULAR GENETIC CHARACTERISTICS**

The early cytogenetic studies on bladder SmCC demonstrated hypertriploidy and hypertetraploidy, and extensive chromosomal rearrangements involving chromosomes 1 to 3, 5 to 7, 9, 11, and 18. Frequent deletions of 4q, 5q, 10q, and 13q, all of which contain loci of tumor suppressor genes, were identified in later comparative genomic hybridization studies. Gains of 5q, 6p, 8q, and 20q were also noted. High-level amplifications were found at 1p22-32, 3q26.3, 8q24, and 12q14-21, genomic sites harboring oncogenes such as c-myc and MDM2.

More recent studies have identified frequent loss of heterozygosity in bladder SmCC at 9p21 (p16), 3p25-26 (VHL), 9q32-33 (DBCl), and 17p13 (TP53). Quantitative studies on the methylation status of RASSF1, MLH1, DAPK1, and MGMT tumor suppressor genes demonstrated that their promoter regions were commonly methylated. The subsequently decreased expression and dysfunction of those tumor suppressor genes may lead to carcinogenesis and the aggressive behavior of bladder SmCC.

Molecular genetic studies have also suggested a common clonal origin for bladder SmCC and coexisting bladder UC. In cases of invasive bladder SmCC, the coexisting UC component is usually also invasive, and all the earlier comparative molecular investigations on the origin of bladder SmCC were focused on these 2 invasive components. Loss of heterozygosity analysis of 5 polymorphic microsatellite markers first demonstrated a common clonality between invasive bladder SmCC and invasive bladder UC; additional X chromosomal inactivation analysis in females illustrated the same nonrandom inactivation in both invasive bladder SmCC and invasive bladder UC, suggesting a common clonal origin. Because UC in situ coexisting with bladder SmCC has been reported in only 14% of the cases, the early stage of bladder SmCC seemed rather elusive. In a recent case study, identical point mutations of TP53 were found in invasive bladder SmCC and coexisting UC in situ; additionally, no loss of heterozygosity of 9 microsatellite markers and TP53alpha was found in either component. This study represented the first molecular evidence for the development of bladder SmCC out of bladder UC in situ.

**DIFFERENTIAL DIAGNOSES**

Small cell carcinoma of the urinary bladder may be mistaken for poorly differentiated UC with scant cytoplasm, malignant lymphoma, or even inflammation in crushed, cauterized, superficial, or scant specimens. Metastasis from the lung or extension from adjacent visceria needs to be ruled out by clinicopathologic correlation because immunohistochemistry often offers only limited assistance. As mentioned, TTF-1 may be expressed in SmCC of multiple anatomic sites, thus it does not necessarily indicate a pulmonary origin.

Distinction between SmCCs of the prostate and urinary bladder may be challenging, especially in small biopsy specimens with no or only scant associated prostatic adenocarcinoma or urothelial carcinoma. Prostate-specific antigen is usually negative in prostatic SmCC, thus a negative prostate-specific antigen stain on tissue or low serum prostate-specific antigen level does not help distinguish prostatic versus urinary bladder origin of SmCC. Other prostate specific immunostains, such as p50ls and prostate-specific membrane antigen, also show low (approximately 20%) positivity rates in prostatic SmCC cases. When there are accompanying epithelial neoplastic components, such as prostatic or urothelial differentiation, attention to their morphology may help determine the primary source. Similarly, dysplastic changes in the adjacent nonneoplastic prostatic or urothelial element may also be helpful. In addition, as mentioned, the recently identified prostatic carcinoma–specific TMRSS2-ERG gene fusion is helpful in confirming a prostatic origin for SmCC; however, the absence of this gene fusion cannot be used to rule out a prostatic origin.

Another diagnostic pitfall is alveolar rhabdomyosarcoma, which may involve the urinary bladder (rare) and has a predilection to occur in adults. It may occur either in pure form or as a component of heterologous differentiation in sarcomatoid UC. These tumors may have significant morphologic overlap with SmCC because the classic “alveolar” architecture may not be appreciated, and the tumor may present with an almost exclusively round cell, primitive appearance. In that case, immunohistochemistry targeting muscular differentiation may be helpful. Rhabdomyoblasts are positive for myogenin, MyoD1, and desmin, but negative for pancytokeratin. Of note, the morphologic overlap is compounded by aberrant synaptophysin immunoreactivity in alveolar rhabdomyosarcoma.

**TREATMENT AND PROGNOSIS**

Data for bladder SmCC treatment regimens are available almost exclusively from retrospective reviews because of the low disease incidence. Such low incidence of SmCC of the urinary bladder has made it difficult to establish definitive treatment algorithms. Most patients present at late stages and, therefore, need multimodal therapy. A number of treatment modalities, including cystectomy, partial cystectomy, radiotherapy, chemotherapy alone, and neoadjuvant/adjuvant chemotherapy, are currently employed. Stage and performance status are the major prognostic determinants.

Transurethral resection of the bladder tumor alone is usually not curative and is associated with survival of 3 to 6 months. Such treatment, alone, is reserved for patients who cannot tolerate more aggressive therapies or for palliation of symptoms only. The bladder-sparing proto-
bladder, in contrast to bladder SmCC, has a more discernable architecture (nests, trabeculae, organoid, pali-hard, and so forth) and shows more prominent nucleoli. Large cell neuroendocrine carcinoma may be pure (vanishingly rare) or admixed with components of urothelial, squamous, glandular, or small cell carcinoma. For pure large cell neuroendocrine carcinoma of the urinary bladder, its response rate to currently available chemotherapy, and correspondingly its prognosis, appears to be similar to those of bladder SmCC, with both entities having a rapidly fatal outcome.©

SUMMARY

Small cell carcinoma of the urinary bladder is a rare, often fatal, disease. Its presenting age, sex predilection, symptoms, and gross morphology are similar to those of conventional urothelial carcinoma, whereas its biologic behavior is much more aggressive when compared with stage-matched urothelial carcinoma. Metastasis is common and prognosis is poor. Small cell carcinoma of the urinary bladder shares similar histomorphologic features with its counterparts in the lungs and other parts of the body. Its immunoreactivity to conventional neuroendocrine markers, however, is comparatively low. Its diagnosis is thus considered permissible on morphologic grounds alone. A few novel differential markers including p16 and p63 have been explored, and the use of immunohistochemical panels has been suggested to distinguish bladder small cell carcinoma from conventional urothelial carcinoma, a distinction carrying therapeutic and prognostic significance. Multimodal treatment is often employed, although no definite treatment algorithm has yet been established. For this extremely aggressive malignancy with an as-yet inconclusive etiology, further studies are needed to clarify its molecular pathogenesis to serve as a basis for diagnostic markers and therapeutic targets.

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OTHER BLADDER NEUROENDOCRINE TUMORS

Neuroendocrine tumors in the urinary bladder besides SmCC include carcinoid tumor, large cell neuroendocrine carcinoma, paraganglioma, and neuroendocrine tumors with other histologic types. Fewer than 10 convincing cases of pure carcinoid tumor and fewer than 10 convincing cases of primary pure large cell neuroendocrine carcinoma of the urinary bladder have been reported, when employing the criteria used for their better-known pulmonary counterparts.©

Reported outcome data on primary pure carcinoid tumor of the urinary bladder are extremely limited and are inadequate to make a reliable inference on prognosis. Large cell neuroendocrine carcinoma of the urinary


