9 Neuroendocrine Tumors of the Urinary Bladder

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Neuroendocrine tumors (NETs) are commonly found in the lung, gastrointestinal tract, and pancreas. NETs of the lung are classified as small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC), and typical and atypical carcinoid tumors. NETs of the gastrointestinal tract and pancreas are subdivided based on their histological differentiation and Ki67 proliferation index into well-differentiated neuroendocrine tumors (WDNETs) grades 1, 2, and 3 or poorly differentiated neuroendocrine carcinomas (NEC) including SCNEC and LCNEC. In the urinary bladder, however, neuroendocrine neoplasms are classified into WDNETs, SCNEC, and LCNEC, in addition to paraganglioma [1]. The cell of origin of these tumors remains uncertain. Neuroendocrine cells found in the basement membrane of normal urothelium or reactive urothelial epithelium may give rise to WDNETs, while less differentiated NETs, including SCNEC and LCNEC, seem to arise from divergent differentiation of urothelial carcinoma [2]. Paragangliomas are thought to arise from chromaffin cells in the autonomic ganglia of the urinary bladder wall [3]. NETs of the urinary bladder are listed in Table 9.1 with clinical and pathologic features.

Well-Differentiated Neuroendocrine Tumors

Although the use of the term "carcinoid tumor" to describe WDNETs in the urinary bladder has been discouraged by the World Health Organization (WHO) [1], this term is still frequently used, especially when describing tumors with malignant features, such as "malignant carcinoid."

Epidemiology, Clinical Features, and Treatment

WDNETs of the urinary bladder are extremely rare, with fewer than 25 cases described in the literature [4]. Based on these few described cases, patient demographics are similar to those of urothelial carcinoma. WDNETs of the urinary bladder typically arise in middle-aged to elderly men who are, in most cases, asymptomatic; the tumors are found incidentally on cystoscopy or imaging studies performed for other reasons. In some cases, patients may present with nonspecific symptoms of hematuria and irritative urinary symptoms or with obstructive symptoms if the tumor is located

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Table 9.1 A summary of the clinical and pathologic features of urinary bladder NETs

	WDNET	SCNEC	LCNEC	Paraganglioma
Clinical features				
Incidence	Extremely rare (~25 cases reported in the literature)	Rare (<1% of bladder tumors), 500 new cases per year	Extremely rare (~30 cases reported in the literature)	Rare (0.6% of bladder tumors)
Age range	Middle-aged to elderly	Elderly	Middle-aged to elderly	Young to middle-aged
Sex predilection	Male	Male	Male	Female
Syndrome association	None known	None known	None known	2/3 are sporadic; 1/3 are associated with inherited disorders (germline mutation in SDHB, VHL, NF-1, Carney triad, MEN 2A and MEN 2B, and familial paraganglioma syndrome)
Symptoms	Asymptomatic (discovered on cystoscopy or imaging performed for other purposes) or obstructive symptoms	Irritative and/or obstructive symptoms, symptoms of metastatic disease, and paraneoplastic syndromes	Irritative and/or obstructive symptoms and symptoms of metastatic disease	Hematuria, hypertension, and micturition syncope in approximately half of the cases, paroxysmal palpitation and diaphoresis less commonly seen
Prognosis	Cured by surgery in majority of cases; 1/4 of cases had aggressive local disease and LN or distant metastasis	Poor (5-year cancer-specific survival rate is 14–16%)	Poor	Cured by surgery in majority of cases; malignant features (extensive local disease and metastasis) in 20% of cases
Hypothesized cell of origin	NE cells found in the basement membrane of normal urothelium or reactive urothelial epithelium	Divergent differentiation of multipotent stem cells in the urothelial lining		Chromaffin cells in autonomic ganglia in the wall of the bladder
Pathologic features				
Gross appearance	Small (0.1–1.2 cm) smooth-surfaced nodules or polyps with hyperemic mucosa, located in the bladder neck or trigone area	Polypoid, nodular, or ulcerated appearance and variable degrees of muscular and perivesical fat invasion		Solitary, well-circumscribed, intravesical exophytic or intramural nodule, 2–5 cm at greatest dimension
Growth pattern	Nested, trabecular, glandular, or acinar architectures with frequent association with cystitis cystica and cystitis glandularis, Usually located in the lamina propria, Rarely involve the muscularis propria	Infiltrative sheets, cords, and occasional geographic necrosis		Characteristic discrete nests (Zellballen) with intervening vascular septa

Cytology	Abundant amphophilic granular cytoplasm (reminiscent of Paneth cells), bland nuclei with speckled chromatin, and absent to inconspicuous nucleoli Rarely, atypical cells with larger nuclei and conspicuous nucleoli can be seen, with rare to no mitoses, and no necrosis	Overlapping, small, round to oval, hyperchromatic nuclei with nuclear molding, speckled chromatin pattern, no or inconspicuous nucleoli, scant cytoplasm, high mitotic rate (>10 mitoses/10 high-power fields); Azzopardi phenomenon can be seen	Large, polygonal cells, low nuclear-cytoplasmic ratio, polymorphic nuclei, coarse chromatin, and prominent nucleoli; mitoses and necrosis are more pronounced than in SCNEC	Polygonal cells that have finely granular amphophilic cytoplasm and ovoid nuclei embedded in a richly vascularized fibrous stroma with sustentacular cells; nuclear pleomorphism and occasional mitotic figures can be seen, but do not reflect signs of malignancy
Immunohistochemistry	syn, chr, NSE, CD56+, c-Kit,CK7,uroplakin,TTF-1,PAP+/−,PSA-	syn, chr, NSE, CD56, INSM1+, CK7, EMA, CAM 5.2, CK, AE1/AE3 mostly + CK 34βE12, GATA3, TTF-1+/−, CK20, uroplakin, CD44v6, PSA, PAP-	syn, chr, NSE, CD56+, CK7, EMA, CAM 5.2, CK, AE1/AE3 mostly+ TTF-1-	Polygonal cells: syn,chr,NSE,CD56,GATA3+,CK,EMA- Sustentacular cells: S-100, SOX10
Ki-67 (Mib-1)	Low	High	High	Variable

NET neuroendocrine tumor, *WDNET* well-differentiated neuroendocrine tumor, *SCNEC* small cell neuroendocrine carcinoma, *LCNEC* large cell neuroendocrine carcinoma, *NE* neuroendocrine, *syn* synaptophysin, *chr* chromogranin, *NSE* neuron-specific enolase, *PAP* prostatic acid phosphatase, *PSA* prostate-specific antigen, *TTF*-1 thyroid transcription factor, *INSM1* insulinoma-associated protein 1, *EMA* epithelial membrane antigen, *CK* cytokeratin

in the bladder outlet or the urethra. WDNETs of the urinary bladder are not hormonally active in most cases, and carcinoid syndrome has not been reported in association with these tumors [5]. However, paraneoplastic syndrome, in the form of calcitonin-producing WDNET, has been reported [6]. The majority of urinary bladder WDNETs behave in a benign fashion; however, cases with aggressive local disease, lymph node and/or distant metastasis, and death due to the disease have been described [1, 5].

Cystoscopic transurethral resection of low-grade WDNETs shows, in the few cases where long-term outcomes have been documented, no recurrence or disease progression [5]. For more aggressive disease, partial or radical cystectomy or cystoprostatectomy with systemic chemotherapy may be required [7, 8].

Pathologic and Immunohistochemical Features

On cystoscopic examination, most cases of WDNETs of the urinary bladder consist of small (0.1–1.2 cm) smooth-surfaced nodules or polyps with hyperemic mucosa located in the bladder neck or trigone area, although larger lesions (up to 5 cm) have been reported [7]. Histologically, WDNETs are usually located in the lamina propria. However, there are rare exceptions where the tumors involve the muscularis propria [9]. WDNETs demonstrate the typical pattern of carcinoid tumors found in other locations: trabecular, insular (Fig. 9.1a), pseudoglandular (Fig. 9.1b), or acinar architecture with frequent association with cystitis cystica and cystitis glandularis [9]. The neoplastic cells of WDNETs

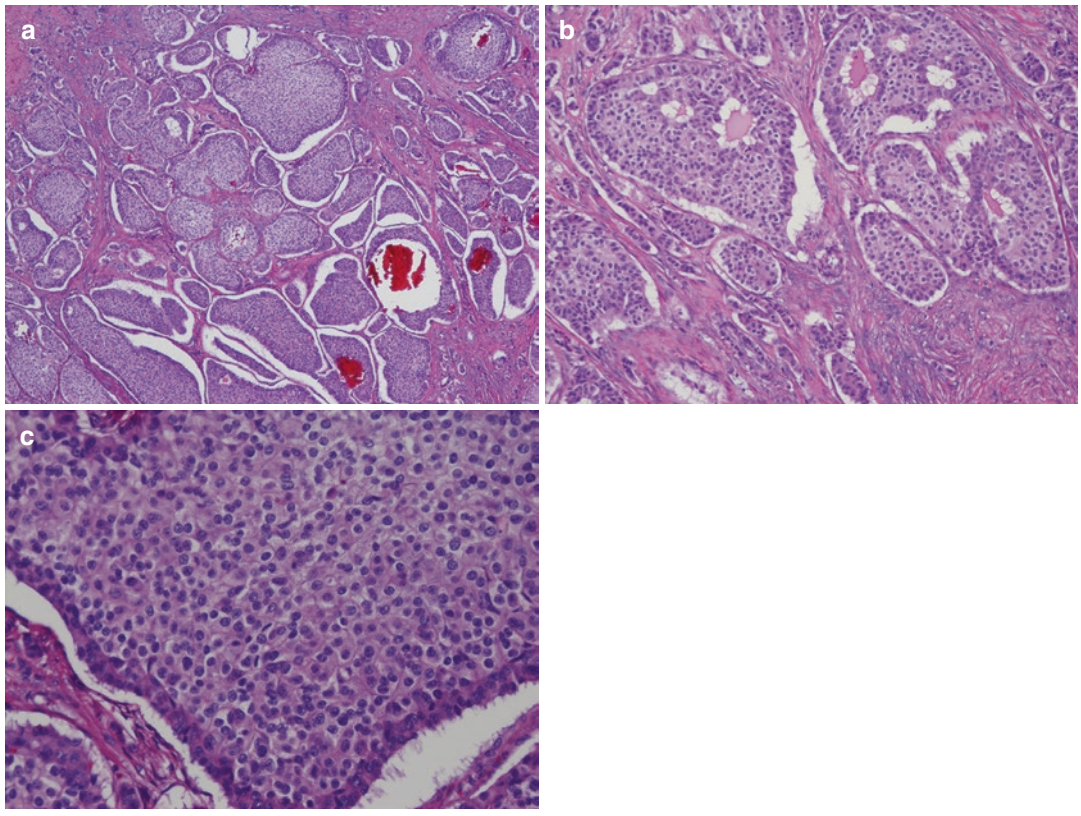

Fig. 9.1 (**a**) WDNET shows insular growth pattern with delicate fibrovascular stroma and artifactual stromal retraction (hematoxylin and eosin, 20x). (**b**) WDNET shows nested pattern with focal pseudoglandular architecture (hematoxylin and eosin, 100x). (**c**) WDNET cells have abundant amphophilic cytoplasm, bland nuclei with speckled chromatin, inconspicuous nucleoli, and no mitoses. Necrosis is not seen (hematoxylin and eosin, 200x)

have abundant amphophilic granular cytoplasm (reminiscent of Paneth cells), bland nuclei with speckled chromatin, and absent to inconspicuous nucleoli. Occasionally, atypical cells with large nuclei and conspicuous nucleoli can be seen. Mitoses are rare, and necrosis is generally absent (Fig. 9.1c). Although no defined criteria have been proposed for malignancy, malignant carcinoid tumors of the urinary bladder have been reported in the literature. In one case, transmural extension, serosal infiltration, and lymph node metastasis were seen [7]. In other cases, distant metastasis to the lungs and bones have been reported [8].

Urinary bladder WDNETs stain with commonly used neuroendocrine markers [synaptophysin, chromogranin, neuron-specific enolase (NSE), CD56, and CD57]. Additionally, some tumors show positive staining with c-Kit (CD117), cytokeratin-7, uroplakin, and thyroid transcription factor (TTF-1) [2, 5, 10]. Also, staining of the tumor cells with prostate acid phosphatase (PAP) presents a potential diagnostic pitfall where WDNETs can be confused with prostatic origin tumors. The lack of staining with other prostate-specific markers, including prostate-specific antigen (PSA) and NKX3.1, can be used to distinguish these entities [9].

In urinary bladder WDNETs, no further classification into grade 1, grade 2, and grade 3 based on a number of mitoses and Ki-67 proliferation index is officially recommended.

Small Cell Neuroendocrine Carcinoma

Epidemiology, Clinical Features, and Treatment

Previously known as oat cell carcinoma, SCNEC of the urinary bladder is more common than WDNET and LCNEC; however, it still only accounts for less than 1% of urinary bladder tumors [11], with approximately 500 new cases per year [2].

SCNECs of the urinary bladder, distinct from pulmonary SCNECs, are usually present as a combined form with urothelial carcinoma and SCNEC, and pure SCNECs are relatively rare. SCNECs typically affect older males with a history of smoking. Hematuria is the most commonly presenting symptom; irritative and obstructive symptoms are less commonly observed [11, 12]. Features of paraneoplastic syndrome, in the form of humoral hypercalcemia of malignancy secondary to the production of parathyroid hormone-related protein, have been observed [13]. Although urinary bladder SCNEC tends to have better prognosis than SCNEC of the lung or prostate [4], neuroendocrine differentiation of urothelial carcinoma confers a worse prognosis, with earlier distant metastases, than does conventional urothelial carcinoma [14, 15]. However, when SCNEC is compared to conventional urothelial carcinoma at similar stage, there is no difference in survival [16]. The 5-year cancer-specific survival rate for SCNEC is 14–16% [17, 18].

Surgical management with cystectomy has an important role in the management of patients with urinary bladder SCNEC, unlike SCNEC of the lung [11, 19–23]. SCNEC patients who receive chemotherapy, radiation therapy, and cystectomy achieve the best overall survival and cancer-specific survival outcomes compared to a single therapeutic modality [24]. Few cases of SCNEC arising in the ureter or the urethra have been reported in the literature, with similar histological features to SCNEC of the urinary bladder [25–27].

Molecular Genetics

These tumors are thought to arise from divergent differentiation of multipotent stem cells in the urothelial lining. This theory is supported by the exceedingly rare incidence of pure SCNEC of the urinary bladder and because these tumors are usually found in association with either urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, or sarcomatoid carcinoma [11, 28–30]. In a series of 51 patients with SCNEC of the urinary bladder, the majority of cases had urothelial carcinoma; few patients had adenocarcinoma or

squamous cell carcinoma components, and only 12% had pure SCNEC without other carcinoma components [31]. Additional studies demonstrated a common clonal origin of coexisting urothelial carcinoma and SCNEC, further substantiating the divergent differentiation model of SCNEC development. SCNEC of the urinary bladder shares common molecular aberrations with SCNEC of pulmonary origin. Deletions in 4q, 5q, 10q, and 13q; DNA gains in 5p, 6p, 8q, and 20q; and loss of heterozygosity in 3p25–26, 9p21, 9q32–33, and 17p13 have all been shown to lead to activation of oncogenes or suppression of tumor suppressor genes in SCNEC of the urinary bladder [32, 33]. Alteration in the tumor suppressor genes, RB1 and TP53, are found in 90% of SCNEC cases of the urinary bladder [16, 34]. However, alterations in these two genes are also prevalent in conventional high-grade urothelial carcinomas, which may lead to the conclusion that these mutations lead to the development of invasive tumors rather than drive neuroendocrine differentiation [35]. Activating mutations in TERT promoter gene are found in urinary bladder SCNEC and conventional urothelial carcinoma, but not lung or prostate SCNEC, further supporting the divergent differentiation model of SCNEC of the urinary bladder [36].

Pathologic Features

On cystoscopic examination, SCNEC can originate from anywhere in the urinary bladder, including urachal remnants. SCNEC has similar cystoscopic and gross pathologic features to urothelial carcinoma, with a polypoid, nodular, or ulcerated appearance; however, muscular and perivesical fat invasion is more commonly seen in SCNEC [4, 11, 37].

Histological examination shows the classical features of SCNEC in other organs, with morphologic triads: (1) small size of tumor cell nuclei (less than three resting lymphocytes (<20 microns); (2) scanty cytoplasm with overlapping, small, round to oval hyperchromatic nuclei and nuclear molding; and (3) speckled or "salt and pepper" chromatin pattern with no or inconspicuous nucleoli (Fig. 9.2a). In addition to these features, SCNECs always show a high mitotic rate (>10 mitoses/10 high-power fields) and single-cell necrosis or large areas of geographic necrosis (Fig. 9.2b and c). When small cell tumors do not show a high mitotic index and/or areas of necrosis, the diagnosis of SCNEC should be reserved for other ancillary diagnostic tests. Smudged, deeply basophilic material deposited in the blood vessels surrounding the tumor cells (Azzopardi phenomenon) can be observed. Most cases show lymphovascular and muscularis propria invasion [11, 14]. Coexisting non-small cell carcinoma components can be difficult to establish on biopsy specimens; however, resection specimens should be thoroughly sampled to look for more differentiated invasive urothelial carcinoma or urothelial carcinoma in situ (Fig. 9.3a and b).

In cases with crush artifacts or poorly prepared sections, non-small cell carcinoma may mimic SCNEC. In such cases, immunohistochemistry should be utilized to properly classify the tumor, as the classification has significant management implications.

Immunohistochemical Features

SCNEC of the urinary bladder typically expresses markers of epithelial and neuroendocrine differentiation. A panel of NSE, CD56, synaptophysin (Fig. 9.3c), and chromogranin (Fig. 9.3d) is typically used to demonstrate neuroendocrine differentiation. These neuroendocrine markers are not always expressed in SCNECs, and diagnosis can be based solely on examination of hematoxylin- and eosin-stained sections [1, 11, 14, 28]. Insulinoma-associated protein 1 (INSM1) is a recently described driver of neuroendocrine differentiation and a marker that has high sensitivity and specificity to neuroendocrine tumors and has been recently reported to be positive in 87% of SCNECs of the urinary bladder [38, 39]. Epithelial markers show variable positivity, with cytokeratin 7 (Fig. 9.3e), epithelial membrane antigen (EMA), cytokeratin AE1/AE3, and cytokeratin CAM 5.2 (perinuclear dot-like positivity) (Fig. 9.3f) seen in the majority of cases and cyto-

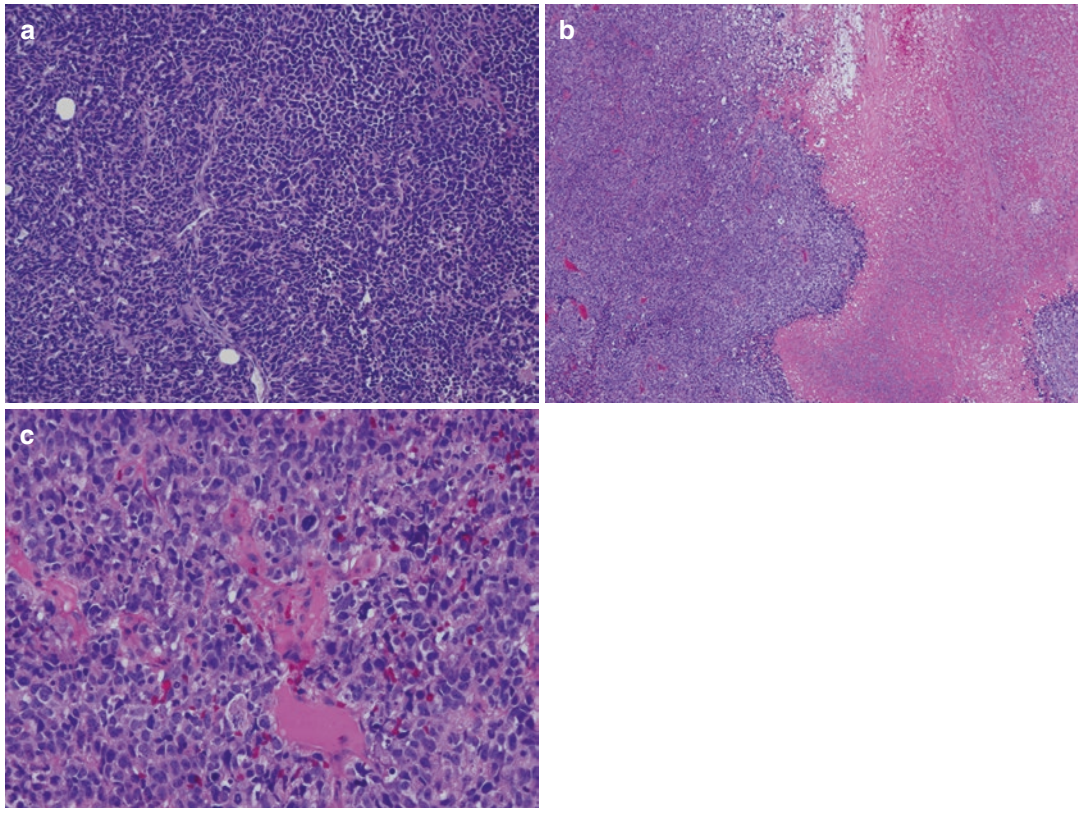

Fig. 9.2 (**a**) SCNEC cells have small nuclei, scanty cytoplasm, nuclear molding, and speckled chromatin pattern with no to inconspicuous nucleoli (hematoxylin and eosin, 100x). (**b**) SCNEC show large areas of geographic necrosis (hematoxylin and eosin, 40x). (**c**) SCNEC shows high mitotic activity (hematoxylin and eosin, 200x)

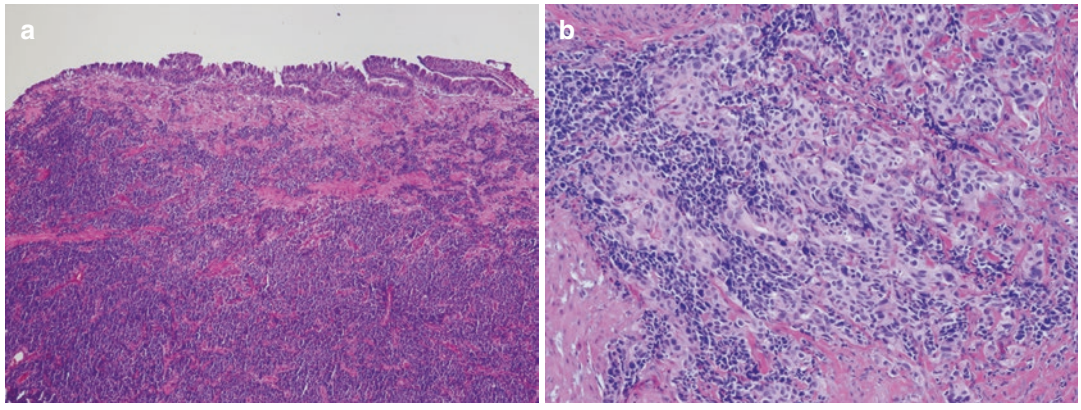

Fig. 9.3 (**a**) SCNEC (deeper in the urinary bladder wall) coexists with urothelial carcinoma in situ (on the surface) (hematoxylin and eosin, 40x). (**b**) SCNEC coexists with conventional invasive high-grade urothelial carcinoma (hematoxylin and eosin, 100x). (**c–g**) The conventional urothelial component from Fig. 9.3b shows positive membranous and cytoplasmic staining with CAM 5.2, CK7, and CK20 and no staining with NE markers. The SCNEC component shows cytoplasmic staining with synaptophysin but no staining with chromogranin. The cytokeratins show perinuclear dot-like positivity with CAM 5.2 and CK7 and no staining with CK20. ((**c**) synaptophysin, 100x; (**d**) chromogranin, 100x; (**e**) cytokeratin 7, 200x; (**f**) cytokeratin CAM 5.2, 200x; and (**g**) cytokeratin 20, 200x)

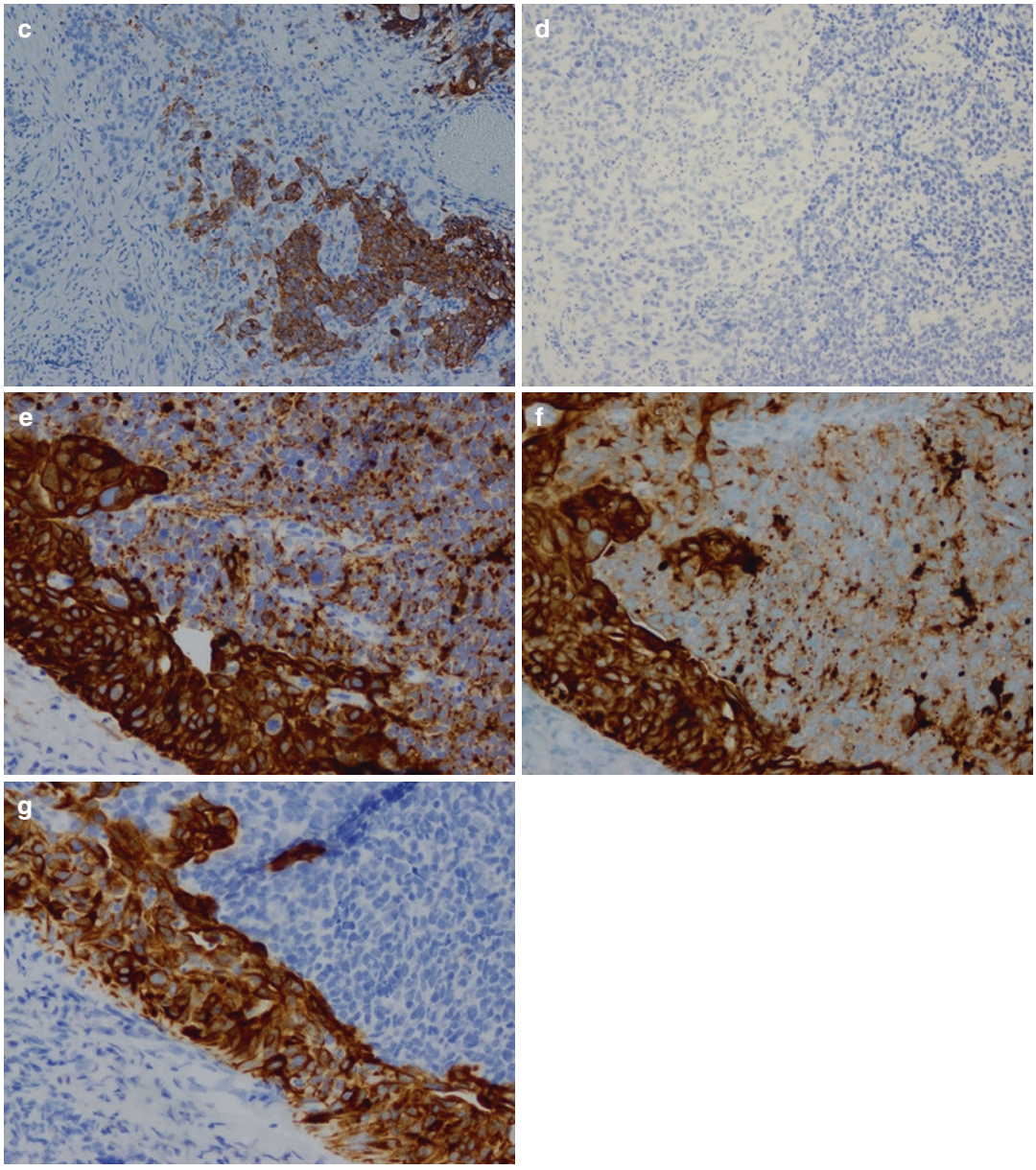

Fig. 9.3 (continued)

keratin 34βE12 in less than half of the cases [11, 14, 15, 28–31, 40–42]. Cytokeratin 20, which is commonly positive in urothelial carcinoma, is typically negative in SCNEC [2] (Fig. 9.3g). GATA3, a marker of conventional urothelial carcinoma, can be seen focally to diffusely positive in approximately one-third of SCNEC; however, this marker should be used with caution in cases of metastatic SCNEC, as lung origin tumors can show focal GATA3 expression in a minority of cases [43]. Uroplakin II and III, other known urothelial markers, mostly do not stain SCNEC [44]. TTF-1 is a marker classically thought to be lung- and thyroid-specific but is also expressed in up to

50% of SCNEC of the urinary bladder [1, 11, 45]. Detected expression of somatostatin receptors (SSTRs) type 2A and type 4 in SCNEC of the urinary bladder has been documented [46]. Varying rates of positivity for P53, P16, epidermal growth factor receptor (EGFR), and c-Kit (CD117) immunohistochemical staining have been documented [11]. Aberrant regulation of CD44 expression, a cell-cell and cell-matrix adhesion molecule, has been correlated with aggressive and metastatic variants of some tumors. The glycoprotein product of the v6 splice variant of CD44 (CD44v6) can be utilized to distinguish poorly differentiated urothelial carcinoma from SCNEC. Poorly differentiated urothelial carcinoma cases will show positive staining with CD44v6, while no staining is typically seen in SCNEC [47]. Differentiating between primary SCNEC of the urinary bladder and SCNEC arising in the prostate and involving the urinary bladder has important clinical implications. In most cases, the presence of a more differentiated, non-neuroendocrine carcinoma component helps in determining the origin of the SCNEC. However, in cases of pure SCNEC, distinguishing urothelial from prostatic origin can be challenging. In such cases, correlation with the clinical and imaging findings, in addition to immunohistochemistry, is required. PSA and PAP expression can be lost in prostatic SCNEC, but not in the more differentiated prostatic adenocarcinoma components. Thus, PSA,PAP, and NKX3.1 staining can be valuable differentiation tools [2, 48, 49]. Additionally, homeobox B13 (HOXB13) has been reported to be a specific and sensitive prostate marker that can be used, especially in poorly differentiated NETs [50].

Large-Cell Neuroendocrine Carcinoma (LCNEC)

Limited data is available regarding the cell of origin of this type of tumors; however, it is believed that LCNEC arises from similar pathways to SCNEC [2, 28].

Epidemiology, Clinical Features, and Treatment

LCNEC of the urinary bladder is rare, with fewer than 30 cases reported in the literature [51]. These tumors have a predilection to older males and generally have aggressive biological behavior and poor prognosis. Cases with pure LCNEC histology have a worse prognosis than cases where more conventional urothelial carcinoma is seen in combination with LCNEC [2, 51, 52]. Octreotide scanning commonly detects more differentiated NETs, but is not typically useful in detecting LCNEC. Thus, more conventional imaging modalities, like contrast-enhanced CT and PET/CT scans, are used in staging and in localizing distant metastasis [19]. Given the rarity of this tumor, treatment plans are based on extrapolation from the literature about pulmonary LCNEC [52].

A single case of primary LCNEC of the ureter has been reported. The tumor showed pure LCNEC morphology and stained with neuroendocrine markers and cytokeratin, but not with uroplakin or TTF-1 [53].

Pathologic and Immunohistochemical Features

Similar to LCNEC in the lung, microscopic examination of LCNEC of the urinary bladder shows neuroendocrine morphology, such as organoid nesting, trabecular growth, rosette-like structures, and peripheral palisading patterns with comedo-type central necrosis. The tumor cells are large and polygonal with low nuclear-cytoplasmic ratio, pleomorphic nuclei, coarse chromatin, and prominent nucleoli [54] (Fig. 9.4a). Mitoses and necrosis are more pronounced in LCNEC than in SCNEC [2]. Like SCNEC, mixed histology with LCNEC and urothelial, squamous, adenocarcinoma, or sarcomatoid carcinoma are commonly encountered [21]. Pure LCNEC is extremely rare. Like other tumors with neuroendocrine features, synaptophysin

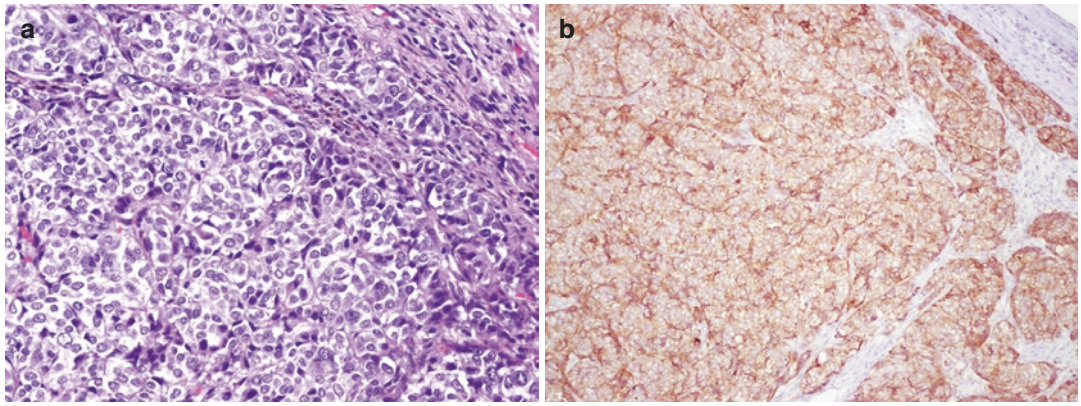

Fig. 9.4 (**a**) LCNEC shows large and polygonal tumor cells with low nuclear-cytoplasmic ratio, polymorphic nuclei, coarse chromatin, and focal prominent nucleoli (hematoxylin and eosin, 100x). (**b**) LCNEC shows cytoplasmic staining with synaptophysin (100x)

(Fig. 9.4b), chromogranin, CD56, and NSE are usually positive in these tumors, along with epithelial markers like cytokeratin AE1/AE3, cytokeratin CAM 5.2, and EMA. Unlike SCNEC, LCNEC of the urinary bladder are not TTF-1-positive [54]. Of note, chromogranin is less sensitive in LCNEC than in SCNEC in the urinary bladder [2]. The exceptionally high Ki-67 index in LCNEC (>95% in some cases), along with positive staining with neuroendocrine markers, serves to confidently distinguish this entity from urothelial carcinoma [54, 55].

The molecular alterations that occur in LCNEC of the urinary bladder have not been studied. Common molecular alterations seen in LCNEC of pulmonary origin, especially those with targetable mutations like EGFR, should be examined in these tumors [56].

Paraganglioma

Extra-adrenal paraganglioma, also known as extra-adrenal pheochromocytoma, is a relatively rare neuroendocrine tumor that arises from chromaffin cells in the autonomic ganglia. In the genitourinary tract, paraganglioma is most common in the bladder but has been reported in the kidney, renal pelvis, ureter, urethra, prostate, spermatic cord, and seminal vesicles [3, 57–64].

Epidemiology, Clinical Features, and Treatment

Despite being the most common site of paraganglioma in the genitourinary tract, urinary bladder paragangliomas represent less than 0.6% of urinary bladder tumors. Unlike other tumors with neuroendocrine differentiation in the urinary bladder, younger females are more likely to develop paragangliomas of the urinary bladder, with a 1:3 male-to-female ratio and a mean age of 45 years [65]. These tumors are either found incidentally on imaging or cystoscopy or present with the classic symptoms of hypertension, hematuria, and micturition syncope in only half of the cases, with paroxysmal palpitation and diaphoresis less commonly seen [19, 66–72].

About two-thirds of the paragangliomas arising in the genitourinary tract are sporadic, and one-third are seen in association with inherited disorders, including germline mutation in succinate dehydrogenase B (SDHB), von Hippel-Lindau disease (VHL), type 1 neurofibromatosis (NF-1), Carney triad, multiple endocrine neoplasia type 2A (MEN 2A) and 2B (MEN 2B), and familial paraganglioma syndrome [3, 73–76].

CT and MRI scans can be used to detect paragangliomas, but both have a lower sensitivity and specificity than radioisotope scanning with ^{131}Iodine metaiodinebenzylguinidine (MIBG)

[66, 67, 77, 78]. Complete surgical resection is the mainstay of treatment in genitourinary paragangliomas [66, 67, 73, 77, 79–81].

Although the majority of paragangliomas have good prognosis and are considered benign, malignant features, defined by metastasis or extensive local disease (i.e., deep local invasion or invasion of adjacent structures, lymph nodes, or distant metastases), are seen in 15–20% of cases. Tumors associated with mutations in SDHB are more likely to show malignant characteristics [2, 65, 73, 82–84].

Pathologic and Immunohistochemical Features

Urinary bladder paragangliomas grossly appear as solitary, well-circumscribed, intravesical exophytic, or intramural nodules that is 2–5 cm in greatest dimension (Fig. 9.5a). The ubiquitous nature of paraganglia in the bladder makes staging such tumors difficult, as paragangliomas arising in the paraganglia present in the muscular wall should not be interpreted as a muscle-invasive tumor (Fig. 9.5b).

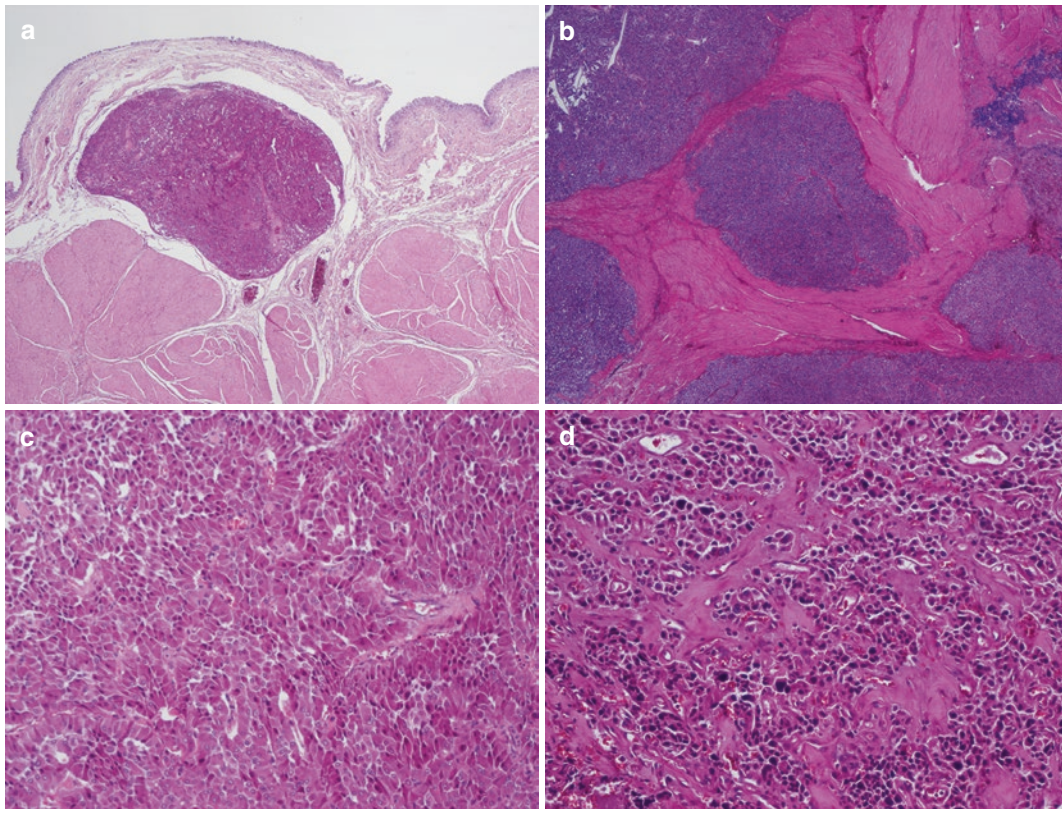

Fig. 9.5 (**a**) Primary urinary bladder paraganglioma forms a well-circumscribed submucosal nodule (hematoxylin and eosin, 20x). (**b**) Primary urinary bladder paraganglioma grows in the muscularis propria. As paraganglia are ubiquitously present in the urinary bladder wall, this should not be interpreted as muscle invasiveness (hematoxylin and eosin, 20x). (**c**) Primary urinary bladder paraganglioma shows polygonal cells with finely granular amphophilic cytoplasm and ovoid nuclei embedded in a richly vascularized stroma (hematoxylin and eosin, 100x). (**d**) Primary urinary bladder paraganglioma cells show nuclear atypia with nuclear pleomorphism and hyperchromasia (hematoxylin and eosin, 100x). (**e**) Primary urinary bladder paraganglioma shows nuclear staining with GATA3 (100x). (**f**) Primary urinary bladder paraganglioma shows cytoplasmic granular staining with synaptophysin (100x)

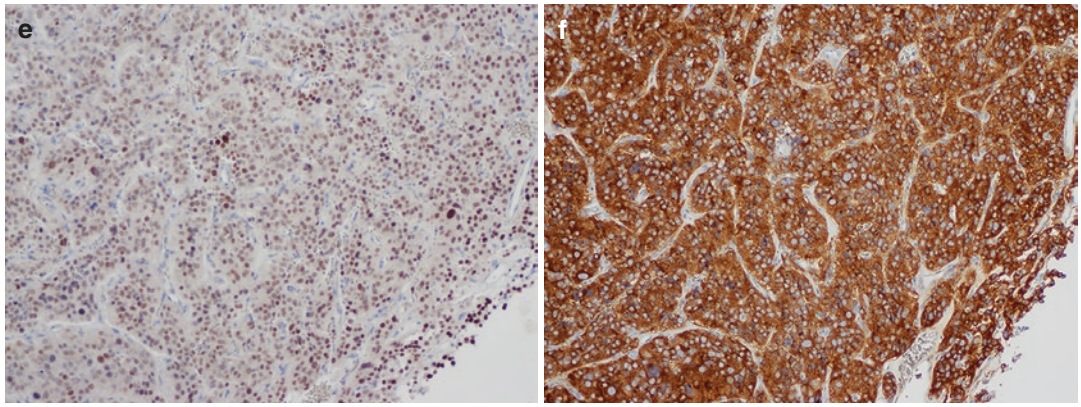

Fig. 9.5 (continued)

Histologically, paragangliomas show the characteristic "zellballen" morphology of paragangliomas elsewhere, with polygonal cells that have finely granular amphophilic cytoplasm and ovoid nuclei embedded in a richly vascularized fibrous stroma (Fig. 9.5c). Nuclear pleomorphism and hyperchromasia (Fig. 9.5d), occasional mitotic figures, and focal neuroblastic or ganglioneuromatous differentiation can be seen, but no correlation has been shown between these parameters and the malignant potential of the tumor [19, 67, 68, 74, 85, 86].

Although the diagnosis of paraganglioma can be readily rendered on hematoxylin- and eosin-stained sections, immunohistochemical stains may be needed for diagnosis in some cases. Bladder paraganglioma can have a histological resemblance to nested variant of urothelial carcinomas or urothelial carcinoma with neuroendocrine differentiation, especially on transurethral resection of bladder tumor (TURBT) specimens. In these cases, the presence of clusters of epithelioid tumor cells with intact normal-appearing urothelium should raise the possibility of paraganglioma. Additionally, cytokeratin and P63 positivity can be used to rule out paraganglioma, as paragangliomas are usually negative for cytokeratin and P63. On the other hand, GATA3, which is typically a urothelial marker, is positive in up to 89% of paraganglioma cases (Fig. 9.5e). This poses a potential pitfall of misdiagnosing paraganglioma as urothelial carcinoma based on GATA3 positivity [87–92].

Like other tumors of neuroendocrine origin, synaptophysin (Fig. 9.5f), chromogranin, and CD56 are positive in paraganglioma; S-100 and SOX10 highlight the sustentacular cells in paraganglioma, but not the polygonal cells, which helps in distinguishing paraganglioma from granular cell tumor of the bladder or melanoma [93]. The use of SDHB immunostain can be used to predict biological behavior. Subsequent mutational analysis can also be performed on cases that show loss of staining with SDHB immunostain [60, 82]. Also see "Paraganglioma" in Chap. 8, Mesenchymal Tumors.

Summary

Although NETs of the bladder are rare, proper recognition of NETs is clinically important, because SCNEC and LCNEC are highly malignant and require different treatment protocols than those for conventional urothelial carcinoma. Carcinoid tumors and paragangliomas, on the other hand, generally have benign and indolent clinical courses, though malignant behavior may sometimes be observed. To make a correct diagnosis of NETs, proper recognition of morphology with judicious immunohistochemical stain selection is required.

References

1. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. Eur Urol. 2016;70(1):93–105. https://doi.org/10.1016/j.eururo.2016.02.029.
2. Kouba E, Cheng L. Neuroendocrine tumors of the urinary bladder according to the 2016 World Health Organization classification: molecular and clinical characteristics. Endocr Pathol. 2016;27(3):188–99. https://doi.org/10.1007/s12022-016-9444-5.
3. Purnell S, Sidana A, Maruf M, Grant C, Agarwal PK. Genitourinary paraganglioma: demographic, pathologic, and clinical characteristics in the surveillance, epidemiology, and end results database (2000–2012). Urol Oncol. 2017;35(7):457.e9–457.e14. https://doi.org/10.1016/j.urolonc.2017.02.006.
4. Posfai B, Kuthi L, Varga L, et al. The colorful palette of neuroendocrine neoplasms in the genitourinary tract. Anticancer Res. 2018;38(6):3243–54. https://doi.org/10.21873/anticancers.12589.
5. Chen Y, Epstein JI. Primary carcinoid tumors of the urinary bladder and prostatic urethra: a clinicopathologic study of 6 cases. Am J Surg Pathol. 2011;35(3):442–6. https://doi.org/10.1097/PAS.0b013e318208f96a.
6. Mascolo M, Altieri V, Mignogna C, Napodano G, De Rosa G, Insabato L. Calcitonin-producing well-differentiated neuroendocrine carcinoma (carcinoid tumor) of the urinary bladder: case report. BMC Cancer. 2005;5:88. https://doi.org/10.1186/1471-2407-5-88.
7. Hemal AK, Singh I, Pawar R, Kumar M, Taneja P. Primary malignant bladder carcinoid— a diagnostic and management dilemma. Urology. 2000;55(6):949. https://doi.org/10.1016/S0090-4295(00)00470-2.
8. Sugihara A, Kajio K, Yoshimoto T, et al. Primary carcinoid tumor of the urinary bladder. Int Urol Nephrol. 2002;33(1):53–7. https://doi.org/10.1023/a:1014400818905.
9. Baydar DE, Tasar C. Carcinoid tumor in the urinary bladder: unreported features. Am J Surg Pathol. 2011;35(11):1754–7. https://doi.org/10.1097/PAS.0b013e31823455eb.
10. Zozumi M, Nakai M, Matsuda I, et al. Primary carcinoid tumor of the urinary bladder with prominent subnuclear eosinophilic granules. Pathol Res Pract. 2012;208(2):109–12. https://doi.org/10.1016/j.prp.2011.10.008.
11. Erdem GU, Özdemir NY, Demirci NS, Şahin S, Bozkaya Y, Zengin N. Small cell carcinoma of the urinary bladder: changing trends in the current literature. Curr Med Res Opin. 2016;32(6):1013–21. https://doi.org/10.1185/03007995.2016.1155982.
12. Sroussi M, Elaidi R, Fléchon A, et al. Neuroendocrine carcinoma of the urinary bladder: a large, Retrospective Study From the French Genito-Urinary Tumor Group. Clin Genitourin Cancer. Published online December 5, 2019. https://doi.org/10.1016/j.clgc.2019.11.014.
13. Sacco E, Pinto F, Sasso F, et al. Paraneoplastic syndromes in patients with urological malignancies. Urol Int. 2009;83(1):1–11. https://doi.org/10.1159/000224860.
14. Schneider NI, Zigeuner R, Langner C. Small cell carcinoma of the urinary bladder: a rare tumor with propensity for hepatic involvement. Am J Med Sci. 2013;345(2):155–7. https://doi.org/10.1097/MAJ.0b013e3182648759.
15. Perán Teruel M, Giménez Bachs JM, Martínez Ruiz J, et al. Neuroendocrine carcinoma of the urinary bladder. 15-year retrospective analysis. Arch Esp Urol. 2012;65(2):237–43.
16. Wang G, Xiao L, Zhang M, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic and immunohistochemical analysis of 81 cases. Hum Pathol. 2018;79:57–65. https://doi.org/10.1016/j.humpath.2018.05.005.
17. Cheng L, Pan C-X, Yang XJ, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. Cancer. 2004;101(5):957–62. https://doi.org/10.1002/cncr.20456.
18. Choong NWW, Quevedo JF, Kaur JS. Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer. 2005;103(6):1172–8. https://doi.org/10.1002/cncr.20903.
19. Fine SW. Neuroendocrine lesions of the genitourinary tract. Adv Anat Pathol. 2007;14(4):286–96. https://doi.org/10.1097/PAP.0b013e3180ca8a89.
20. Smith J, Reidy-Lagunes D. The management of extrapulmonary poorly differentiated (high-grade) neuroendocrine carcinomas. Semin Oncol. 2013;40(1):100–8. https://doi.org/10.1053/j.seminoncol.2012.11.011.
21. Thompson S, Cioffi-Lavina M, Chapman-Fredricks J, Gomez-Fernandez C, Fernandez-Castro G, Jorda M. Distinction of high-grade neuroendocrine carcinoma/small cell carcinoma from conventional urothelial carcinoma of urinary bladder: an immunohistochemical approach. Appl Immunohistochem Mol Morphol. 2011;19(5):395–9. https://doi.org/10.1097/PAI.0b013e31820eca9a.
22. Pant-Purohit M, Lopez-Beltran A, Montironi R, MacLennan GT, Cheng L. Small cell carcinoma of the urinary bladder. Histol Histopathol. 2010;25(2):217–21. https://doi.org/10.14670/HH-25.217.
23. Vetterlein MW, Wankowicz SAM, Seisen T, et al. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. Cancer. 2017;123(22):4346–55. https://doi.org/10.1002/cncr.30907.
24. Niu Q, Lu Y, Xu S, et al. Clinicopathological characteristics and survival outcomes of bladder neuroendocrine carcinomas: a population-based study. Cancer Manag Res. 2018;10:4479–89. https://doi.org/10.2147/CMAR.S175286.
25. Kanagarajah P, Ayyathurai R, Saleem U, Manoharan M. Small cell carcinoma arising from

the bulbar urethra: a case report and literature review. Urol Int. 2012;88(4):477–9. https://doi.org/10.1159/000332154.
26. Acosta AM, Kajdacsy-Balla A. Primary neuroendocrine tumors of the ureter: a short review. Arch Pathol Lab Med. 2016;140(7):714–7. https://doi.org/10.5858/arpa.2015-0106-RS.
27. Kim TS, Seong DH, Ro JY. Small cell carcinoma of the ureter with squamous cell and transitional cell carcinomatous components associated with ureteral stone. J Korean Med Sci. 2001;16(6):796–800. https://doi.org/10.3346/jkms.2001.16.6.796.
28. Pompas-Veganzones N, Gonzalez-Peramato P, Sanchez-Carbayo M. The neuroendocrine component in bladder tumors. Curr Med Chem. 2014;21(9):1117–28.
29. Ploeg M, Aben KK, Hulsbergen-van de Kaa CA, Schoenberg MP, Witjes JA, Kiemeney LA. Clinical epidemiology of nonurothelial bladder cancer: analysis of the Netherlands Cancer registry. J Urol. 2010;183(3):915–20. https://doi.org/10.1016/j.juro.2009.11.018.
30. Grignon DJ, Ro JY, Ayala AG, et al. Small cell carcinoma of the urinary bladder. A clinicopathologic analysis of 22 cases. Cancer. 1992;69(2):527–36.
31. Abrahams NA, Moran C, Reyes AO, Siefker-Radtke A, Ayala AG. Small cell carcinoma of the bladder: a contemporary clinicopathological study of 51 cases. Histopathology. 2005;46(1):57–63. https://doi.org/10.1111/j.1365-2559.2004.01980.x.
32. Terracciano L, Richter J, Tornillo L, et al. Chromosomal imbalances in small cell carcinomas of the urinary bladder. J Pathol. 1999;189(2):230–5. https://doi.org/10.1002/(SICI)1096-9896(199910)189:2<230::AID-PATH407>3.0.CO;2-8.
33. Cheng L, Jones TD, McCarthy RP, et al. Molecular genetic evidence for a common clonal origin of urinary bladder small cell carcinoma and coexisting urothelial carcinoma. Am J Pathol. 2005;166(5):1533–9.
34. Chang MT, Penson A, Desai NB, et al. Small-cell carcinomas of the bladder and lung are characterized by a convergent but distinct pathogenesis. Clin Cancer Res. 2018;24(8):1965–73. https://doi.org/10.1158/1078-0432.CCR-17-2655.
35. Wang Y, Li Q, Wang J, et al. Small cell carcinoma of the bladder: the characteristics of molecular alterations, treatment, and follow-up. Med Oncol. 2019;36(12):98. https://doi.org/10.1007/s12032-019-1321-x.
36. Zheng X, Zhuge J, Bezerra SM, et al. High frequency of TERT promoter mutation in small cell carcinoma of bladder, but not in small cell carcinoma of other origins. J Hematol Oncol. 2014;7(1):47. https://doi.org/10.1186/s13045-014-0047-7.
37. Sjödahl G. Molecular subtype profiling of urothelial carcinoma using a subtype-specific immunohistochemistry panel. Methods Mol Biol. 1655;2018:53–64. https://doi.org/10.1007/978-1-4939-7234-0_5.
38. Kim IE, Amin A, Wang LJ, Cheng L, Perrino CM. Insulinoma-associated protein 1 (INSM1) expression in small cell neuroendocrine carcinoma of the urinary tract. Appl Immunohistochem Mol Morphol. Published online December 23, 2019. https://doi.org/10.1097/PAI.0000000000000824.
39. Lan MS, Breslin MB. Structure, expression, and biological function of INSM1 transcription factor in neuroendocrine differentiation. FASEB J. 2009;23:2024–33.
40. Soriano P, Navarro S, Gil M, Llombart-Bosch A. Small-cell carcinoma of the urinary bladder. A clinico-pathological study of ten cases. Virchows Arch. 2004;445(3):292–7. https://doi.org/10.1007/s00428-004-1041-1.
41. Blomjous CE, Vos W, Schipper NW, De Voogt HJ, Baak JP, Meijer CJ. Morphometric and flow cytometric analysis of small cell undifferentiated carcinoma of the bladder. J Clin Pathol. 1989;42(10):1032–9. https://doi.org/10.1136/jcp.42.10.1032.
42. Blomjous CE, Vos W, De Voogt HJ, Van der Valk P, Meijer CJ. Small cell carcinoma of the urinary bladder. A clinicopathologic, morphometric, immunohistochemical, and ultrastructural study of 18 cases. Cancer. 1989;64(6):1347–57. https://doi.org/10.1002/1097-0142(19890915)64:6<1347::aid-cncr2820640629>3.0.co;2-q.
43. Bezerra SM, Lotan TL, Faraj SF, et al. GATA3 expression in small cell carcinoma of bladder and prostate and its potential role in determining primary tumor origin. Hum Pathol. 2014;45(8):1682–7. https://doi.org/10.1016/j.humpath.2014.04.011.
44. Li W, Liang Y, Deavers MT, et al. Uroplakin II is a more sensitive immunohistochemical marker than uroplakin III in urothelial carcinoma and its variants. Am J Clin Pathol. 2014;142(6):864–71. https://doi.org/10.1309/AJCP1J0JPJBPSUXF.
45. Paner GP, Lopez-Beltran A, Sirohi D, Amin MB. Updates in the pathologic diagnosis and classification of epithelial neoplasms of urachal origin. Adv Anat Pathol. 2016;23(2):71–83. https://doi.org/10.1097/PAP.0000000000000110.
46. Fernández-Aceñero MJ, Córdova S, Manzarbeitia F, Medina C. Immunohistochemical profile of urothelial and small cell carcinomas of the bladder. Pathol Oncol Res. 2011;17(3):519–23. https://doi.org/10.1007/s12253-010-9341-z.
47. Iczkowski KA, Shanks JH, Bostwick DG. Loss of CD44 variant 6 expression differentiates small cell carcinoma of urinary bladder from urothelial (transitional cell) carcinoma. Histopathology. 1998;32(4):322–7. https://doi.org/10.1046/j.1365-2559.1998.00398.x.
48. Neşe N, Kumbaraci BS, Baydar DE, et al. Small cell carcinomas of the bladder highly express somatostatin receptor type 2A: impact on prognosis and treatment—a multicenter study of Urooncology society, Turkey. Appl Immunohistochem Mol Morphol. 2016;24(4):253–60. https://doi.org/10.1097/PAI.0000000000000188.

49. Gurel B, Ali TZ, Montgomery EA, et al. NKX3.1 as a marker of prostatic origin in metastatic tumors. Am J Surg Pathol. 2010;34(8):1097–105. https://doi.org/10.1097/PAS.0b013e3181e6cbf3.
50. Varinot J, Cussenot O, Roupret M, et al. HOXB13 is a sensitive and specific marker of prostate cells, useful in distinguishing between carcinomas of prostatic and urothelial origin. Virchows Arch. 2013;463(6):803–9. https://doi.org/10.1007/s00428-013-1495-0.
51. Akdeniz E, Bakirtas M, Bolat MS, Akdeniz S, Özer I. Pure large cell neuroendocrine carcinoma of the bladder without urological symptoms. Pan Afr Med J. 2018;30:134. https://doi.org/10.11604/pamj.2018.30.134.13437.
52. Martín IJP, Vilar DG, Aguado JM, et al. Large cell neuroendocrine carcinoma of the urinary bladder. Bibliographic review. Arch Esp Urol. 2011;64(2):105–13.
53. Watson GA, Ahmed Y, Picardo S, et al. Unusual Sites of High-Grade Neuroendocrine Carcinomas: A Case Series and Review of the Literature. Am J Case Rep. 2018;19:710–23. https://doi.org/10.12659/AJCR.908953.
54. Sari A, Ermete M, Sadullahoğlu C, Bal K, Bolükbaşi A. Large cell neuroendocrine carcinoma of urinary bladder; case presentation. Turk Patoloji Derg. 2013;29(2):138–42. https://doi.org/10.5146/tjpath.2013.01165.
55. Radović N, Turner R, Bacalja J. Primary "Pure" Large Cell Neuroendocrine Carcinoma of the Urinary Bladder: A Case Report and Review of the Literature. Clinical Genitourinary Cancer. 2015;13(5):e375–e377. https://doi.org/10.1016/j.clgc.2015.03.005.
56. Colarossi C, Pino P, Giuffrida D, et al. Large cell neuroendocrine carcinoma (LCNEC) of the urinary bladder: a case report. Diagn Pathol. 2013;8:19. https://doi.org/10.1186/1746-1596-8-19.
57. Liu C, Mo C-Q, Jiang S-J, Pan J-C, Qiu S-P, Wang D-H. Primary paraganglioma of seminal vesicle. Chin Med J. 2016;129(13):1627–8. https://doi.org/10.4103/0366-6999.184471.
58. Liu H-W, Liu L-R, Cao D-H, Wei Q. Paraganglioma in the renal pelvis. Kaohsiung J Med Sci. 2014;30(6):319–20. https://doi.org/10.1016/j.kjms.2013.04.007.
59. Awasthi NP, Kumari N, Krishnani N, Goel A. "Functional" paraganglioma of ureter: an unusual case. Indian J Pathol Microbiol. 2011;54(2):405–6. https://doi.org/10.4103/0377-4929.81631.
60. Alataki D, Triantafyllidis A, Gaal J, et al. A non-catecholamine-producing sympathetic paraganglioma of the spermatic cord: the importance of performing candidate gene mutation analysis. Virchows Arch. 2010;457(5):619–22. https://doi.org/10.1007/s00428-010-0966-9.
61. Yi C, Han L, Yang R, Yu J. Paraganglioma of the renal pelvis: a case report and review of literature. Tumori. 2017;103(Suppl. 1):e47–9. https://doi.org/10.5301/tj.5000677.
62. Kwon A-Y, Kang H, An HJ, et al. Spermatic cord paraganglioma with histologically malignant features. Urology. 2016;93:e7–8. https://doi.org/10.1016/j.urology.2016.03.014.
63. Alvarenga CA, Lopes JM, Vinagre J, et al. Paraganglioma of seminal vesicle and chromophobe renal cell carcinoma: a case report and literature review. Sao Paulo Med J. 2012;130(1):57–60.
64. Alberti C. Urology pertinent neuroendocrine tumors: focusing on renal pelvis, bladder, prostate located sympathetic functional paragangliomas. G Chir. 2016;37(2):55–60.
65. Cheng L, Leibovich BC, Cheville JC, et al. Paraganglioma of the urinary bladder: can biologic potential be predicted? Cancer. 2000;88(4):844–52. https://doi.org/10.1002/(sici)1097-0142(20000215)88:4<844::aid-cncr15>3.0.co;2-i.
66. Adraktas D, Caserta M, Tchelepi H. Paraganglioma of the urinary bladder. Ultrasound Q. 2014;30(3):233–5. https://doi.org/10.1097/RUQ.0000000000000113.
67. Liang J, Li H, Gao L, Yin L, Yin L, Zhang J. Bladder paraganglioma: clinicopathology and magnetic resonance imaging study of five patients. Urol J. 2016;13(2):2605–11.
68. Feng N, Li X, Gao H-D, Liu Z-L, Shi L-J, Liu W-Z. Urinary bladder malignant paraganglioma with vertebral metastasis: a case report with literature review. Chin J Cancer. 2013;32(11):624–8. https://doi.org/10.5732/cjc.012.10317.
69. Pichler R, Heidegger I, Klinglmair G, et al. Unrecognized paraganglioma of the urinary bladder as a cause for basilar-type migraine. Urol Int. 2014;92(4):482–7. https://doi.org/10.1159/000348829.
70. Hanji AM, Rohan VS, Patel JJ, Tankshali RA. Pheochromocytoma of the urinary bladder: a rare cause of severe hypertension. Saudi J Kidney Dis Transpl. 2012;23(4):813–6. https://doi.org/10.4103/1319-2442.98167.
71. Bagchi A, Dushaj K, Shrestha A, et al. Urinary bladder paraganglioma presenting as micturition-induced palpitations, dyspnea, and angina. Am J Case Rep. 2015;16:283–6. https://doi.org/10.12659/AJCR.891388.
72. She HL, Chan PH, Cheung SCW. Urinary bladder paraganglioma in a post-heart transplant patient. Ann Acad Med Singap. 2012;41(8):362–3.
73. Martucci VL, Lorenzo ZG, Weintraub M, et al. Association of urinary bladder paragangliomas with germline mutations in the SDHB and VHL genes. Urol Oncol. 2015;33(4):167.e13–20. https://doi.org/10.1016/j.urolonc.2014.11.017.
74. Ranaweera M, Chung E. Bladder paraganglioma: A report of case series and critical review of current literature. World J Clinic Cases. 2014;2(10):591. https://doi.org/10.12998/wjcc.v2.i10.591.
75. Rednam SP, Erez A, Druker H, et al. Von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood.

Clin Cancer Res. 2017;23(12):e68–75. https://doi.org/10.1158/1078-0432.CCR-17-0547.
76. Raygada M, Pasini B, Stratakis CA. Hereditary paragangliomas. Adv Otorhinolaryngol. 2011;70:99–106. https://doi.org/10.1159/000322484.
77. Wang H, Ye H, Guo A, et al. Bladder paraganglioma in adults: MR appearance in four patients. Eur J Radiol. 2011;80(3):e217–20. https://doi.org/10.1016/j.ejrad.2010.09.020.
78. Bosserman AJ, Dai D, Lu Y. Imaging characteristics of a bladder wall paraganglioma. Clin Nucl Med. 2019;44(1):66–7. https://doi.org/10.1097/RLU.0000000000002324.
79. Bishnoi K, Bora GS, Mavuduru RS, Devana SK, Singh SK, Mandal AK. Bladder paraganglioma: safe and feasible management with robot assisted surgery. J Robot Surg. 2016;10(3):275–8. https://doi.org/10.1007/s11701-016-0573-0.
80. Stigliano A, Lardo P, Cerquetti L, et al. Treatment responses to antiangiogenetic therapy and chemotherapy in nonsecreting paraganglioma (PGL4) of urinary bladder with SDHB mutation: a case report. Medicine (Baltimore). 2018;97(30):e10904. https://doi.org/10.1097/MD.0000000000010904.
81. Nayyar R, Singh P, Gupta NP. Robotic management of pheochromocytoma of the vesicoureteric junction. JSLS. 2010;14(2):309–12. https://doi.org/10.4293/108680810X12785289145042.
82. Park S, Kang SY, Kwon GY, et al. Clinicopathologic characteristics and mutational status of succinate dehydrogenase genes in paraganglioma of the urinary bladder: a multi-institutional Korean study. Arch Pathol Lab Med. 2017;141(5):671–7. https://doi.org/10.5858/arpa.2016-0403-OA.
83. Papathomas TG, de Krijger RR, Tischler AS. Paragangliomas: update on differential diagnostic considerations, composite tumors, and recent genetic developments. Semin Diagn Pathol. 2013;30(3):207–23. https://doi.org/10.1053/j.semdp.2013.06.006.
84. Maeda M, Funahashi Y, Katoh M, Fujita T, Tsuruta K, Gotoh M. Malignant bladder pheochromocytoma with SDHB genetic mutation. Aktuelle Urol. 2013;44(5):381–2. https://doi.org/10.1055/s-0033-1345147.
85. Beilan J, Lawton A, Hajdenberg J, Rosser CJ. Locally advanced paraganglioma of the urinary bladder: a case report. BMC Res Notes. 2013;6:156. https://doi.org/10.1186/1756-0500-6-156.
86. Iwamoto G, Kawahara T, Tanabe M, et al. Paraganglioma in the bladder: a case report. J Med Case Rep. 2017;11(1):306. https://doi.org/10.1186/s13256-017-1473-2.
87. Menon S, Goyal P, Suryawanshi P, et al. Paraganglioma of the urinary bladder: a clinicopathologic spectrum of a series of 14 cases emphasizing diagnostic dilemmas. Indian J Pathol Microbiol. 2014;57(1):19–23. https://doi.org/10.4103/0377-4929.130873.
88. Miettinen M, McCue PA, Sarlomo-Rikala M, et al. GATA3: a multispecific but potentially useful marker in surgical pathology: a systematic analysis of 2500 epithelial and nonepithelial tumors. Am J Surg Pathol. 2014;38(1):13–22. https://doi.org/10.1097/PAS.0b013e3182a0218f.
89. Nonaka D, Wang BY, Edmondson D, Beckett E, Sun C-CJ. A study of gata3 and phox2b expression in tumors of the autonomic nervous system. Am J Surg Pathol. 2013;37(8):1236–41. https://doi.org/10.1097/PAS.0b013e318289c765.
90. So JS, Epstein JI. GATA3 expression in paragangliomas: a pitfall potentially leading to misdiagnosis of urothelial carcinoma. Mod Pathol. 2013;26(10):1365–70. https://doi.org/10.1038/modpathol.2013.76.
91. Ghafoor A-U-R, Yousaf I, Pervez R, Khan RU, Mir K. Paraganglioma of urinary bladder: an unusual presentation. Pitfalls in diagnosis and treatment. J Pak Med Assoc. 2012;62(1):63–5.
92. Grignon DJ, Ro JY, Mackay B, et al. Paraganglioma of the urinary bladder: immunohistochemical, ultrastructural, and DNA flow cytometric studies. Hum Pathol. 1991;22(11):1162–9.
93. Ranaweera M, Chung E. Bladder paraganglioma: a report of case series and critical review of current literature. World J Clin Cases. 2014;2(10):591–5. https://doi.org/10.12998/wjcc.v2.i10.591.