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Neuroendocrine Tumors of the Urinary Bladder According to the 2016 World Health Organization Classification: Molecular and Clinical Characteristics

Erik Kouba[1] · **Liang Cheng**[1,2]

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Abstract Neuroendocrine neoplasms of the urinary bladder are a rare type of tumor that account for a small percentage of urinary bladder neoplasms. These tumors of the urinary bladder range from well-differentiated neuroendocrine neoplasms (carcinoids) to the more aggressive subtypes such as small cell carcinoma. Despite the rarity of the neuroendocrine tumors of the bladder, there has been substantial investigation into the underlying genomic, molecular, and the cellular alterations within this group of neoplasms. Accordingly, these findings are increasingly incorporated into the understanding of clinical aspects of these neoplasms. In this review, we provide an overview of recent literature related to the 2016 World Health Organization Classification of Neuroendocrine Tumors of the Urinary Bladder. Particular emphasis is placed on molecular alterations and recently described gene expression. The neuroendocrine tumors of the urinary bladder are subdivided into four subtypes. Similar to their pulmonary and other extrapulmonary site counterparts, these have different degrees of neuroendocrine differentiation and morphological features. The clinical aspects of four subtypes of neuroendocrine tumor are discussed with emphasis of the most recent developments in diagnosis, treatment, and prognosis. An understanding of molecular basis of neuroendocrine tumors will provide a base of knowledge for future investigations into this group of unusual bladder neoplasms.

Keywords Bladder · Neuroendocrine tumors · Molecular genetic classification · Small cell carcinoma · Paraganglioma · Carcinoid · 2016 World Health Organization (WHO) classification

Introduction

Neuroendocrine tumors of the urinary bladder are rare and comprise <1 % of all urinary bladder malignancies. The tumors tend to affect older men, clinical presentations remarkably similar to other types of invasive urothelial carcinoma [1, 2]. The most common presenting clinical signs are hematuria and irritative voiding symptoms [3]. Diagnosis methods are also similar and include transurethral biopsy or resection of the lesion. Characterization is performed primarily on morphology and immunohistochemical stains if needed [4].

The 2016 World Health Organization Classification of Tumors of Urinary System and Male Genital Organ classification system separates four subtypes of neuroendocrine tumors of the urinary bladder and provides a convenient platform to base discussion of the relevant details of the aforementioned: small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, well-differentiated neuroendocrine tumor, and paragangliomas (Table 1) [5]. Due to the rarity of tumors, systematic studies are retrospective in nature and few in number. In this review, we use a similar taxonomy of the neuroendocrine tumors of the bladder and provide an expansive discussion of the genomic, cellular, and clinical aspects of each entity.

✉ Liang Cheng
liang_cheng@yahoo.com

[1] Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, 350 West 11th Street, IUHPL Room 4010, Indianapolis, IN 46202, USA

[2] Department of Urology, Indiana University School of Medicine, Indianapolis, USA

Table 1 2016 WHO Classification of neuroendocrine tumors of the urinary bladder

Neuroendocrine tumors of the urinary tract	Synonym(s)
Small cell neuroendocrine carcinoma	Neuroendocrine carcinoma
	Oat cell carcinoma (obsolete)
Large cell neuroendocrine carcinoma	None
Well-differentiated neuroendocrine tumor	Carcinoid tumor
Paraganglioma	Extraadrenal pheochromocytoma

Small Cell Neuroendocrine Carcinoma (Small Cell Carcinoma) of the Urinary Bladder

Small cell carcinoma of the urinary bladder is one of the more common of the neuroendocrine tumors of the urinary bladder with an estimated 500 cases per year or 0.14 cases per 100,000 people [1, 2]. On microscopic examination, the tumor consists of sheets or nests of small or intermediate cells with molding, scant cytoplasm, inconspicuous nucleoli, and evenly dispersed "salt-and-pepper chromatin" (Fig. 1) [6, 7]. Mitotic activity is usually brisk and frequent crush artifact is found. Necrosis is commonly present as is vascular invasion (Table 2) [4, 8].

Small cell carcinoma of the bladder affects patients over the age of 60 with a male predominance [9–16]. The most common presenting symptom is hematuria with voiding symptoms, and rarely can paraneoplastic syndromes accompany the tumor [17, 18]. Approximately 60 % of patients present with metastatic disease at time of diagnosis [7]. Although rarely small cell carcinoma presents diagnostic difficulties, other entities must be considered in the differential diagnosis including lymphoma, poorly differentiated urothelial carcinoma, poorly differentiated squamous cell carcinoma, small cell carcinoma from other sites, and lymphoepithelioma-like carcinoma [4]. Small cell carcinoma of the urinary bladder typically exhibits both epithelial and neuroendocrine differentiation. Immunohistochemical stains show high positivity for chromogranin, synaptophysin, CD57 (Leu7) CD56, TTF-1, neuron-specific enolase, CAM5.2, Keratin7, and epithelial membrane antigen (EMA). Additionally, GATA3 has been found in 32 % of tumors (Table 3) [4, 7, 19–24]. Additionally, immunohistochemical stains such as CK20 are negative in small cell carcinoma, but positive in 40–70 % of urothelial carcinomas. Also, CK20 can be used to distinguish Merkel cell carcinoma (positive) from small cell carcinomas of the urinary bladder (negative). The distinction between lymphoma and small cell carcinoma is made by a positive CD45 (LCA), negative neuroendocrine, and negative epithelial profile. The distinction between prostate and bladder origin of small cell carcinoma can be more difficult, especially in smaller biopsy specimens. PSA is usually negative and p501S has a low staining rate (20 %). The prostate-specific TMPRss2-ERG fusion can rule in prostate origin, but negative staining does not rule it out [4, 25, 26].

The original theories of the cells of origin in small cell carcinoma included a tumor arising from a Kultschitzky-type cell or a tumor arising from a cell that is not normally present in the urinary bladder mucosa [27]. Cheng et al. showed

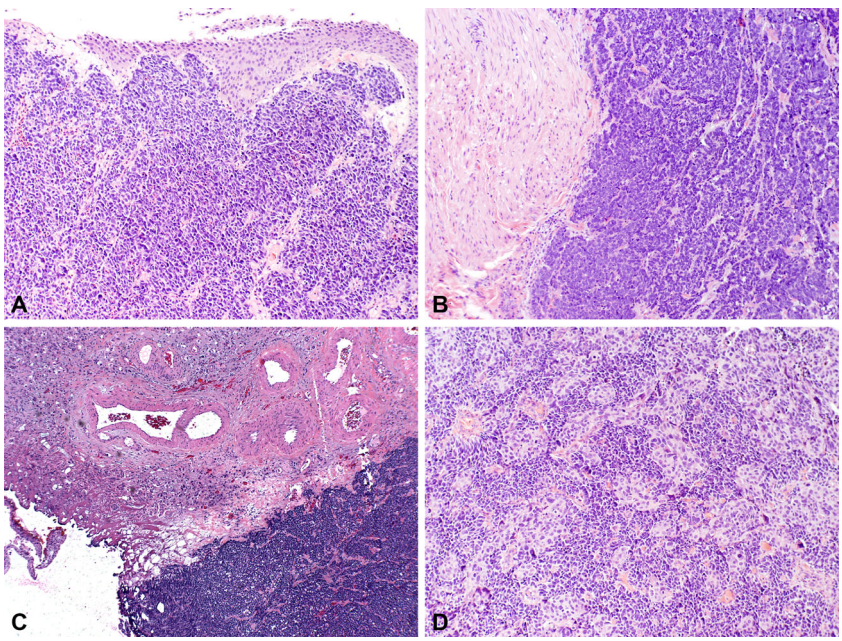

Fig. 1 Small cell carcinoma of the urinary bladder. The cells show sheets of hyperchromatic cells with molding, scant cytoplasm, and inconspicuous nucleoli. **a** Invasive suburothelial small cell carcinoma. Lamina propria is lined with normal urothelium. **b** Invasive small cell carcinoma of the urinary bladder invading large bundles of muscularis propria. **c** Coexistence of invasive small cell carcinoma with invasive urothelial carcinoma showing a distinct zonal pattern. **d** Coexistence of invasive small cell carcinoma with invasive urothelial carcinoma showing an intermingled nested pattern

Table 2 Morphological features of neuroendocrine tumors of the urinary bladder

Features	Small cell neuroendocrine carcinoma	Large cell neuroendocrine carcinoma	Well-differentiated neuroendocrine tumor (carcinoid)	Paraganglioma
Architecture	Diffuse sheets	Sheets	Anastomosing cords	Nests
	Nests	Solid nests	Glandular	Diffuse growth
		Trabeculae Rosettes	Cribriform structures	Pseudorosettes
Cellular shape				
Fusiform	Common	Rare	Absent	Absent
Polygonal with abundant cytoplasm	Absent	Typical	Absent	Frequent
Cuboidal/columnar	Absent	Absent	Frequent	Rare
Cell size	Small/intermediate	Large	Intermediate	Large
Cytoplasm (amount)	Scant	Abundant	Moderate	Moderate
Nuclei				
Size	Small	Large	Small	Medium
Shape	Round to oval	Oval	Round to oval	Round to oval
Molding	Frequent	Absent	Absent	Absent
Crush artifact	Typical	Rare	Absent	Absent
Chromatin	Finely granular	Coarse, granular, vesicular	Finely stippled	Smudged, hyperchromatic
Nucleolus	Salt and pepper Inconspicuous	Prominent	Inconspicuous	Prominent
Other findings				
Necrosis	Frequent	Large areas	Absent	Rare
Mitotic activity	High	Very high	Low	Rare

molecular genetic evidence of common clonal origin of co-existing small cell carcinoma of the urinary bladder suggesting that the cell of origin was a multipotential, undifferentiated cell or stem cell [28].

Genetic studies have identified the frequent loss of heterozygosity in 9p21 (*p16*), 3p25–26 (*VHL*), 9q32–33 (*DBC1*), and 17p13 (*TP53*) [28, 29]. Quantitative studies performed on the methylation status of *RASSSF1*, *MLH1*, *DAPK1*, *TERT*, and *MGMT* tumor suppressor genes found a high incidence of promotor region methylation [30–32]. Subsequent decrease and/or dysfunction of those tumor suppressor genes may lead to unregulated carcinogenesis [33, 34]. More recently, a unique promotor mutation in the *TERT* gene was identified and found to be a unique mutation from other sites of small cell carcinoma. Immunohistochemical stains show high positivity for chromogranin, synaptophysin, CD56, TTF-1, neuron-specific enolase, CAM5.2, Keratin7, and EMA. Additionally, GATA3 has been found in 32 % of tumors (Table 3) [4, 7, 19–24].

The treatment includes a multimodal approach with some of the longest disease-free survivals occurring in the setting of neoadjuvant (platinum-based) chemotherapy [17, 35]. Other approaches combine partial cystectomy or radical cystectomy with adjuvant chemotherapy [36–38]. Chemotherapy regimens have been extrapolated from the pulmonary counterpart and consist of cisplatin, gemcitabine, isofosfamide, and paclitaxel as first-line agents for patients presenting with extensive disease [39–41]. The survival depends on the stage of presentation; however, most of the outcome data is based on retrospective, small series using various nonstandardized treatment modalities. This makes an identification of subgroups for which a particular therapy modality is appropriate [17].

For treatment of limited disease, a number of potential strategies exist; the optimal therapy has not been defined due to lack of controlled studies. Although transurethral resection of the bladder tumor is an initial diagnostic measure for the disease, it does not appear to be sufficient in terms of control of disease due to the aggressive nature. Several retrospective studies have shown worse long-term outcomes of transurethral resection compared to transurethral resection plus cystectomy. The difference in 5-year overall survival between these modalities ranges from 0–16 to 18–36 %. However, there is inherent bias present in patients not undergoing cystectomy due to comorbidities [3, 42, 43].

Platinum-based neoadjuvant chemotherapy and cystectomy have been shown to provide tumor downstaging and control of micrometastases and lead to improved survival. A retrospective study by Siefker-Radtke et al. in 2004 showed

Table 3 Reported ranges of positive immunohistochemical stains in neuroendocrine tumors of the urinary bladder

Immunohistochemical stain	Small cell neuroendocrine carcinoma (%)	Large cell neuroendocrine carcinoma (%)	Carcinoid (%)	Paraganglioma (%)
Neuroendocrine markers				
Chromogranin A	0–100	75	100	90
Synaptophysin	15–100	80–92	100	66
Neuron-specific enolase (NSE)	0–100	90	100	100
CD56	70–80	80	100	
CD57 (Leu7)	30–55	100	100	
Serotonin	77–91			
Epithelial markers				
KeratinAE1/AE3	70–80	87		0
CAM5.2	47–66	100		
CK34BE12	46			
p63	0–10			
Keratin7	50–64		75	0
Keratin20	0		0	0
EMA	0–78	70–100		
Other markers				
TTF-1	0–75	0–25	20	
Uroplakin	0		33	
CD44v6	7			
S-100	40	0		100
CD117	22–28		82	
EGFR	36–50			
PDGFR	100			
Ki67 index	15–80	67		0–7
p16	93			
p53	50–80			5
c-erbB2	50		50	
CD45	3			
GATA3	32			83–100
Vimentin				63
PSAP				Rare

the 5-year disease-specific survival rate to be significantly increased with neoadjuvant chemotherapy compared to cystectomy alone (78 versus 36 %, respectively) [44]. A later study by Lynch et al. found improved survival in patients treated with neoadjuvant chemotherapy compared to cystectomy (160 versus 18 months, respectively) [45]. Another SEER database study found that chemotherapy improved patient survival in localized-stage, regional-stage, and distant-stage disease in conjunction with transurethral resection. The study showed no difference in survival with cystectomy or not [43]. Other clinicopathological parameters such as age, gender, presenting symptoms, and the presence of nonsmall cell carcinoma components do not appear to impact the outcomes in several studies [3, 4, 20]. Currently, the National Comprehensive Cancer Network (NCCN) guidelines state that patients with small cell carcinoma of the bladder are best treated with neoadjuvant chemotherapy followed by radiation or cystectomy [46]. However, prospective, well-controlled studies of the treatment are needed to address the major role treatment modalities to optimize survival outcomes.

In patients presenting with extensive disease, chemotherapy is the mainstay of treatment using cisplatin, gemcitabine, ifosfamide, and paclitaxel as first-line agents. The addition of chemotherapy extends the overall survival from 4 to 8–15 months, respectively [47, 48]. In selected patients with extensive disease, neoadjuvant chemotherapy and cystectomy have shown to have improved survival [45]. Despite chemotherapy and local treatment, distant metastases occur early within the first 6 months after presentation [25]. For relapse,

second-line chemotherapy agents can be used such as cyclophosphamide, vincristine, and doxorubicin [49].

Unlike small cell carcinoma of the lung, with a high incidence of brain metastases (60 %), small cell of the urinary bladder has a lower incidence (10 %). The high rates in pulmonary small cell carcinoma support prophylactic radiation, but the lower incidence and lack of data regarding effects on disease and quality of life preclude this treatment in small cell carcinoma of the urinary bladder [50, 51].

Large Cell Neuroendocrine Carcinoma of the Urinary Bladder

Similar to small cell carcinoma of the urinary bladder, the diagnosis of large cell neuroendocrine tumors of the urinary bladder is established on morphologic criteria similar for the pulmonary counterpart (Fig. 2). This criterion includes large cells, polygonal shape, low nuclear to cytoplasmic ratio, coarse chromatin, and prominent nucleoli. Nuclear palisading and rosettes have been noted (Table 2) [52, 53]. Additionally, immunochemical or ultrastructural evidence of neuroendocrine differentiation is required [54]. The tumor has a high mitotic count and high Ki67 proliferation index with reports of 40 % [15, 24]. Interestingly, the pulmonary literature has shown similar findings as in the bladder: there is no clear nuclear or cell size cutoff between large and small cell carcinoma and high variability in cell size making diagnosis difficult [53, 55].

There are a number of theories for the cell of origin for large cell neuroendocrine carcinoma. The first are similar hypotheses common to the other neuroendocrine tumors of the urinary bladder including multipotent stem cells, originating from the submucosa neuroendocrine cells or urinary tract epithelial metaplasia [26]. Another hypothesis is that the neuroendocrine cells originate from the urachal epithelium [56, 57].

Although there have been no studies of the genomic landscape of large cell neuroendocrine tumors of the urinary bladder due to their rarity, the difference in mutational genes between pulmonary small cell and large cell neuroendocrine carcinoma has been explored. Distinct differential mutations between the two were found in *JAK3*, *NRAS, RB1*, and *VHL* (all absent in large cell and all present in small cell). Other mutational differences include *IDH*, *FGFR1*, *FGFR2*, *KDR*, *KRAS*, and *MET* [58]. Additional studies in the pulmonary literature show common mutations in *TP53*, among the entities [59]. Moreover, chromosomal patterns in large cell carcinoma have demonstrated some similar complex abnormal patterns (4q-, 5q-, 10q-, 13q-, 15q-) to those of small cell carcinoma [60]. Similar to the urinary bladder, investigations of molecular perturbations have focused on small cell carcinoma. Future research is certainly needed to investigate molecular alterations in large cell neuroendocrine tumors of the urinary bladder extrapolated from the pulmonary literature [61].

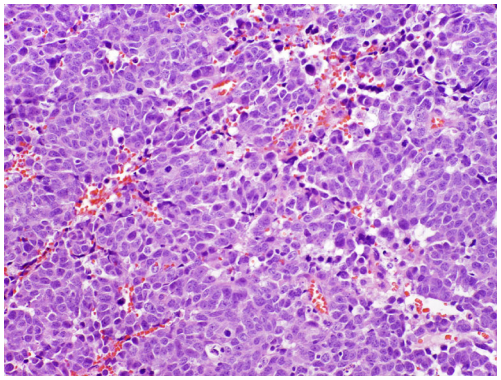

Fig. 2 Large cell neuroendocrine carcinoma of the urinary bladder. The cells show a polygonal shape, coarse chromatin, and prominent nucleoli

The index case of large cell neuroendocrine carcinoma of the urinary bladder was described by Abenoza et al. in 1986 [62]. This neuroendocrine tumor is of high grade, biologically aggressive, and associated with poor prognoses. The presentation is similar to other urinary bladder cancer with gross hematuria being the usual presenting symptom. Additionally, large cell neuroendocrine carcinoma is often admixed with a squamous or adenocarcinoma component [56]. There is a male predominance and old age at presentation [63]. Similar to small cell carcinoma, the diagnosis of the urinary bladder is established on criteria similar for the pulmonary counterpart [54]. As discussed, immunochemical or ultrastructural evidence of neuroendocrine differentiation is required [54]. The tumors show immunohistochemical evidence of neuroendocrine differentiation such as positive staining with chromogranin-A, CD56, and synaptophysin (Table 3). These stains have a combined sensitivity and specificity of 96 and 100 %, respectively, to distinguish neuroendocrine from urothelial carcinoma. However, chromogranin-A staining has a reduced sensitivity for large cell neuroendocrine carcinoma compared to small cell carcinoma (40 versus 80 %, respectively). Not surprisingly, the Ki67 index >40 % has been shown to be 80 % sensitive and 86 % specific to distinguish large cell neuroendocrine carcinoma and urothelial carcinoma [53, 64].

Recognition of the entity is important because of the subsequent poor outcomes. There are no standardized staging protocols; a few scattered reports demonstrate potential utility of positron emission tomography (PET) and computed tomography (CT) for large and small cell neuroendocrine carcinoma [65, 66]. Due to the scarcity of reported cases, there is no standard treatment; however, multimodal therapy with surgery and chemotherapy has been used. A single institution series published by Gupta et al. showed a difference in five patients with large cell neuroendocrine carcinoma treated with adjuvant chemotherapy versus surgery alone (116 versus 2 to 29 months, respectively) [53]. Treatment of these rare bladder

tumors have been largely extrapolated from the pulmonary literature. Chemotherapy extrapolated from pulmonary large cell neuroendocrine carcinoma including a platinum-based regimen is the mainstay [67]. A case in the literature used detection of the EGFR mutation which responds to Gefitinib in order to guide treatment. Other reports use a combination of surgery, radiation, and/or chemotherapy [61, 63, 68].

Distant metastases are frequent, either at diagnosis or later in the course of disease with liver and bone being the most common sites [15, 63]. A case report described a cutaneous metastatic deposit in addition to a reported case of presenting symptom of large cell neuroendocrine carcinoma being neurological symptoms from a brain metastasis. The lack of clinical symptoms related to the bladder lesion is quite unusual. It is unknown what the true incidence is due to rarity of the disease, and extrapolation from the pulmonary literature suggests a high risk with worse outcomes than small cell carcinoma [69–71].

Well-Differentiated Neuroendocrine Tumors (Carcinoids) of the Urinary Bladder

Primary well-differentiated neuroendocrine tumors of the bladder (carcinoids) are very rare with the first case reported by Colby in 1980 [72] and hitherto approximately 10 subsequent cases described in the literature [2, 73] Well-differentiated neuroendocrine tumors (carcinoid) exhibit the same microscopic features described in other sites, that is, uniform cells with finely stippled chromatin and inconspicuous nucleoli with intracytoplasmic granules resembling Paneth cells (Table 1). A unique feature is the arrangement of cells in a pseudoglandular pattern and association with cystitis cystica and cystitis glandularis. Less commonly, well-differentiated neuroendocrine tumors of the urinary bladder are composed of anastomosing cords and nests. An oncocytic variant with cells similar to a renal oncocytoma has been reported along with intraluminal mucin and intracytoplasmic mucin. Additionally, subnuclear eosinophilic granules have been observed (similar to those observed in neuroendocrine tumors of the intestine). Overall, mitotic activity is rare with necrosis absent [24, 74–77].

Well-differentiated neuroendocrine tumors of the urinary bladder contain argyrophilic and argentaffin neurosecretory granules. Cells within the normal bladder urothelium have neuroendocrine features, and chromogranin and serotonin immunoreactivity has been identified in cells in Von Brunn's nests, cystitis glandularis, and cystitis cystica [78]. Several cases of well-differentiated neuroendocrine tumors of the urinary bladder have been found to have features of intracytoplasmic eosinophilic granules (which stain for neuroendocrine markers) and polypoid-like stalks with chronic inflammation, cystitis cystica, and cystitis glandularis, in one study (9 of 13 specimens) [14, 73, 76]. As such, it has been postulated that well-differentiated neuroendocrine tumors of the urinary bladder may arise from the increased number of neuroendocrine cells in these reactive lesions [14, 73, 79]. However, there has been one report of a case with several unique features including location in the trigone and without cystitis glandularis and cystitis cystica and without intracytoplasmic eosinophilic granules [80].

Due to their rarity, the genomic landscape of large cell neuroendocrine tumors (carcinoids) of the urinary bladder has not been explored. Again, we can use the pulmonary counterparts to extrapolate potential alterations. One study showed that the main genes involved with chromatin remodeling were mutated: *ARID2*, *SETD1B*, and *STAG1* [81]. Chromosomal alterations of pulmonary carcinoids showed chromosomal imbalances in 10q and 13q [60]. Future research is certainly needed to identify extrapolations obtained from the pulmonary literature.

Hematuria is the most common presenting symptom with tumors most commonly presenting as small polypoid lesions in bladder neck and trigone. These polypoid-like structures show marked venous engorgement over the tumor and range in size from 3 to 12 mm in greatest dimension [82]. Several cases occurring in the prostatic urethra have also been reported. There is no association with the carcinoid tumor syndrome seen in other body sites. There is one reported case of calcitonin-secreting carcinoid of the urinary bladder; the remainders show no similar paraneoplastic secretion syndromes. The reported range of and gender of patients are similar to conventional urothelial carcinoma [14, 73, 78, 80, 83]. In addition to expressing immunohistochemical neuroendocrine expression, well-differentiated neuroendocrine tumors of the urinary bladder express prostate-specific acid phosphatase but no other prostate markers (Table 3). The prognosis is excellent of typical well-differentiated neuroendocrine tumors limited to the lamina propria. Moreover, involvement of the muscularis propria by well-differentiated neuroendocrine tumors also appears resulting in favorable outcomes, albeit with conclusions based on shorter clinical follow-up [73, 80, 84].

The treatment for localized disease is similar to the treatment of carcinoids at other body sites and primarily involves surgical resection with clinical follow-up [74]. Previous reports suggest that more than 25 % of patients will present with regional or distant spread [82]. Although the pure well-differentiated neuroendocrine tumors of the bladder appear to have excellent prognosis, the number of cases is small with limited follow-up periods. Long-term follow-up for the patient is recommended [80]. Mixed carcinoid tumors appear to exhibit aggressive behavior, with the noncarcinoid driving clinical outcomes [85, 86].

Paraganglioma of the Urinary Bladder

Primary paraganglioma of the bladder is very rare and makes up less than 0.05 % of all bladder malignancies and <1 % of all paragangliomas [1, 87]. The morphological features of a paraganglioma (extra-adrenal pheochromocytoma) are also morphologically similar to other locations of extra-adrenal pheochromocytomas (Fig. 3). The morphology includes the nested growth pattern. Pseudorosette formations exist which are separated by a delicate plexiform vascular or fibrous septa (Table 2). The cells are large and polygonal with amphophilic cytoplasm. Nuclei are usually central but can often be eccentrically located. They can sometimes be pleomorphic and hyperchromatic with smudged chromatin. Mitoses hemorrhage or necrosis is rare [1, 24, 87–91].

The origin of paraganglioma of the urinary bladder is also uncertain but believed to be related to migration of small nests of paraganglionic tissue along the aortic axis and in the pelvic regions into the bladder wall during embryogenesis [92–94]. The paraganglioma originates from the neural crest-derived chromaffin cells of the sympathetic system within the bladder wall [91, 95]. In support of this hypothesis, an autopsy study of 409 patients identified paraganglia in the urinary bladder wall in 52 % cases. The study also showed that paraganglia was present within the different layers of the wall with a predilection for anterior and posterior walls. The muscularis propria of the bladder wall was the commonest location [96].

Approximately, one third of paragangliomas are associated with the inherited mutations in 17 genes. The most important are the von Hippel-Lindau (*VHL*), rearranged during transfection *(RET)*; neurofibromatosis 1 (*NF1*); succinate dehydrogenase (*SDH*) subunits A, B, C, and D; SDH complex assembly factor 2 (*SDHAF2*); transmembrane protein 127 (*TMEM127*); and *myc*-associated factor X genes [97]. More recently, it has been recognized that there are germline mutations in *SDHB* and *SDHD* genes and those who harbor such mutations are more likely to develop paraganglioma and malignant disease. These mutations in *SDHD* tend to be nonsense mutations, whereas in *SDHB* gene the mutations show a broad spread across exons 2–7 [98–100]. Those with germline mutations also show an age-related penetrance and show to be more aggressive [95].

Recent studies have shown that immunohistochemical stains for *SDHB* on routine formalin-fixed tissue paragangliomas can reveal the presence of *SDHB*, *SDHC*, or *SDHD* germline mutations with a high degree of reliability regardless of the type of mutational status, whether missense, nonsense, splice site, or frameshift. These studies revealed the absence of *SDHB* staining in paragangliomas (and pheochromocytomas) with mutations in *SDHB*, *SDHC*, or *SDHD*. Conversely, *SDHB* staining was seen in all cases of tumors related to MEN2, VHL disease, or NF1 and in paragangliomas with

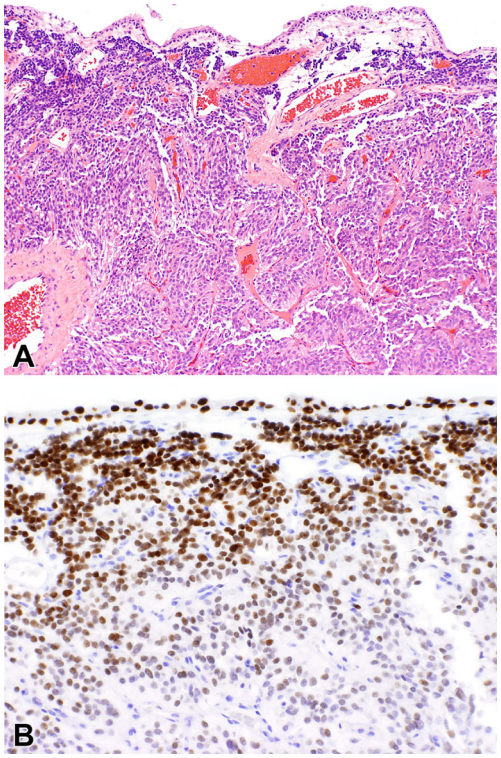

Fig. 3 Paraganglioma of the urinary bladder. **a** The tumor is located submucosally. The cells are arranged in a nested pattern surrounded by a fine vasculare network. The cells are polygonal and have a amphophilic cytoplasm and centrally located nuclei. **b** Positive nuclear GATA3 immunohistochemical stain in paragangliomas of the urinary bladder

no syndromic germline mutation [101, 102]. This follows results of other studies showing that whatever SDH subunit is mutated, inactivation induces a complete abolition of SDH enzyme activity in the tumor suggesting a conformational change or destabilization or proteolysis [103, 104]. The importance of studying the SDHB gene in both inherited and sporadic cases has recently come to light, and the importance lies in genetic counseling and subsequent treatment. For a patient with a paraganglioma in the urinary bladder, immunohistochemical stain negative for *SDHB* is directly related to a germline or somatic mutation. Genetic testing is recommended for those who have negative staining [95, 105].

For sporadic bladder, paragangliomas studies have found frequent chromosomal imbalances with frequent gains at 11cen~q13 and losses at 1p and 3q. Additionally, losses at 22q and 1q32 have been identified. These regions encompass the *PTCH2* gene and tumor suppressor genes which have been implicated in other solid tumors such as meningioma, medulloblastoma, and basal cell carcinoma, among others [106–108]. Furthermore, with regards to individual prognostication, malignant transformation may be associated with increased karyotypic complexity. Currently, future studies are needed to clarify the role of degree of karyotypic complexity for such predictions [106].

Recent studies have shed light into the functional interdependence between genomic and epigenetic landscape of paragangliomas (and pheochromocytomas). Sequencing and high-throughput technologies have been recently used to examine large-scale genomic deletions, amplifications, gene expression, microRNA profiles, and epigenetic alterations thereby improving the characterization of paragangliomas [109–112]. This integrative genomic analysis provides evidence for strong concordance between multiomics data and genetic status and demonstrates that the predisposing maturations discussed in the preceding paragraphs (*SDHx, VHL, RET, NF1*) act as main drivers of the genetic landscape of paragangliomas and pheochromocytomas. The genomic analysis found that the genetic, epigenetic, and transcriptional changes can be clustered into five subtypes based on four fundamental genetic characteristics: (1) genetic mutations, (2) copy-number alterations, (3) methylation patterns, and (4) miRNA expression. The clustered five subtypes also appear to be associated with different clinical outcomes. This integrative analysis with subtypes clearly defined by unique genomic alterations creates a potential for precise molecular classification by molecular methods. Furthermore, outcomes may be predicted based upon these tumoral genomic landscapes [111, 113–115].

Paragangliomas of the urinary bladder can present at any age (range 11–84 years) with a mean age of 45 years and with slight female sex predilection in women [13, 88, 91, 106]. The tumors can also present in childhood populations, albeit rare with 12 cases reported in the literatures ranging in age from 7 to 16 years [116]. Most paragangliomas of the urinary bladder are solitary and localized submucosally to the dome or trigone of the bladder [13, 88, 91]. The tumors have a mean size of 3.9 cm and range from 1.0 to 9.1 cm at presentation [91]. The majority of bladder paragangliomas are hormonally active and can present with clinical symptoms secondary to catecholamine release with micturition attacks such as headaches, hypertension, palpitations, diaphoresis, and blurred vision before or during voiding [13, 95, 97, 106]. Despite such symptoms, the levels of catecholamines in plasma and urine can be normal with an abnormally increased rise in plasma catecholamines only found directly after micturition [13]. However, nonfunctioning paragangliomas are rarer and more difficult to diagnose during their nonsecreting nature [117–119]. In most cases, gross hematuria is a presenting symptom [88].

Immunohistochemical stains are usually positive for NSE, chromogranin, and synaptophysin and negative for keratin (Table 3) [120, 121]. Additionally, S100 stains the sustentacular cells of the tumor [89]. Placing the tumor in Zenker's fixative will turn the tumor black, the so-called positive chromaffin reaction [90]. GATA-3 staining has been found in a majority of paragangliomas, regardless of site [122]. Paragangliomas can be misdiagnosed as urothelial carcinoma due to frequent involvement with muscularis propria, artifactual changes associated from the transurethral resection, and the few distinct symptoms that may prompt the diagnosis (especially in cases of nonfunctioning paragangliomas). Additionally, the overlapping GATA-3-positive staining could potentially contribute to a misdiagnosis [122]. One study showed a misdiagnosis for muscle invasive urothelial carcinoma in consultation cases of near 30 %. In these cases, a diffuse growth pattern simulated the growth pattern of invasive urothelial carcinoma; in other case, the nested pattern mimicked the nested variant of urothelial carcinoma [89, 117, 119]. Others have also written some of the diagnostic difficulties resulting from cautery artifact with necrosis and note that three of five patients at their institution were originally misdiagnosed (two as urothelial carcinoma and one as rhabdomyosarcoma). Oftentimes, paragangliomas have an abundant melanin pigment, which should keep melanoma in the differential [123].

There is no reliable way to distinguish between benign and malignant tumors, and the distinction has long been contentious. The only widely accepted and definitive proof of malignancy is metastasis to other organs. Some histological features such as tumor necrosis, mitotic rate greater than three mitotic figures per 30 high-power fields, capsular invasion, large nests with central degeneration, and cytological pattern of spindle cells are suggestive of increased malignant predilection [87, 89, 90, 95, 117]. Some authors have suggested that DNA ploidy analysis, *p53* alteration, or Ki67 index may be predictive of outcome; however, the clinical outcomes did not support such indicators [87, 91, 124]. However, these findings have not been found to be seen in most cases and may not be a reliable marker in separating benign from malignant paraganglioma [87, 124]. The studies examining malignant versus benign are limited by the small number of cases reported in the literature (approximately 20). However, as discussed in the earlier molecular section, molecular testing might be useful for future subtyping of the tumors with an accompanying clinical prognosis.

Suspected cases of paraganglioma should first be investigated by measuring the levels of catecholamine and metabolites such as metanephrine and vanillylmandelic acid secretion in either blood or urine. However, in cases of nonfunctional paragangliomas, the metabolites may be normal. Imaging can be used to evaluate the primary tumor as well as metastatic lesions. CT imaging has a high sensitivity for detecting extra-adrenal pheochromocytomas which show marked enhancement if the tumor is less than 4 cm. There is good discriminatory power over the more common epithelial neoplasms of the bladder which are characteristically poorly enhanced [88]. The use of

intravenous contrast, however, may precipitate a hypertensive crisis, although nonionic contrast is reported to be safe [90]. Magnetic resonance imaging (MRI) can be helpful with the characteristic appearance of the lesion recently being radiographically characterized based on the multiplanar T1 and T2 dynamic contrast images [125]. Additional imaging modalities especially the I-131-MIBG or I-123-MIBG (iodine-131 (-123)-meta-methyl iodobenzylguanidine) scans or PET can be useful for characterization of both primary and metastatic lesions. The iodine-MIBG scans use a radiolabeled guanethidine analog that resembles norepinephrine and thus accumulates in sympathetic tissue such as paragangliomas [13, 88, 117, 119].

Currently, there is no staging system for bladder paragangliomas. Some have reported using the pheochromocytoma system recommended by the National Cancer Institute (NCI) dividing patients into three categories: localized, regional, and metastatic disease [91]. Paragangliomas can be treated in a number of ways including catecholamine blockade, surgery, and chemotherapy or radiation therapy. Standard treatments are limited by the lack of high-quality data allowing organizational guidelines to publish treatment guidelines. Partial cystectomy was found to be the treatment in 70 % of patients in one series with a 20 % recurrence rate. From the largest review of the literature, the metastatic rate of bladder paragangliomas is 10 %; these have been treated effectively with cyclophosphamide, vincristine, and dacarbazine (the Averbuch protocol). Radiation has also been incorporated using I-123-MIBG radiation [91, 126, 127].

Conclusions

The 2016 World Health Organization Classification of Tumors of Urinary System and Male Genital Organ classification system separates four subtypes of neuroendocrine tumors of the urinary bladder and provides a convenient platform for discussion of the relevant details of the aforementioned. The four members of this family of tumors include small cell carcinoma, large cell neuroendocrine, well-differentiated neuroendocrine, and paragangliomas. The overall prognosis for urinary bladder cancers is worse compared to urothelial carcinoma despite the similar clinical presentations, demographics, risk factors, and diagnostic measures. Furthermore, the rarity of these tumors has not provided an opportunity to perform well-designed, prospective trials for means of treatment. However, with increased investigations into the genetic and cellular alterations, it is hoped that subsequent advances in clinical characterization, prognostication, and treatment will occur for neuroendocrine tumors of the urinary bladder.

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