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Review Article

Neuroendocrine tumors of genitourinary tract: Recent advances

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ABSTRACT

Primary neuroendocrine tumors of the genitourinary tract are rare and are comprised of a heterogeneous group of neoplasms. These include paraganglioma, well-differentiated neuroendocrine tumors or carcinoid tumors, small-cell neuroendocrine carcinoma, and large-cell neuroendocrine carcinoma. Personal experiences, in addition to the findings of an extensive literature search for pertinent publications, were used to compile the epidemiological data, clinical information, histopathological features, prognostic factors, and therapeutic approaches. We also include molecular alterations and targeted treatments of the various neuroendocrine tumors of the genitourinary tract.

1. Background

Neuroendocrine (NE) tumors (NETs) of the genitourinary (GU) tract can be primary or metastatic in origin. Primary NETs of the GU tract constitute a heterogeneous group of neoplasms that fall in a spectrum from indolent well-differentiated NETs to aggressive neuroendocrine carcinomas (NECs). With few exceptions, primary NETs of the GU tract are rare. Different hypotheses have been proposed to explain the origin and pathogenesis of such tumors, including derivation from naturally-occurring diffuse NE cells in the GU tract or derivation from multipotent stem cells. Like their lung, gastrointestinal (GI) tract and pancreatobiliary counterparts, NETs in the GU tract are generally categorized into well-differentiated tumors (carcinoid), and high-grade small cell NECs (small-cell neuroendocrine carcinoma (SCNEC) and large-cell neuroendocrine carcinoma (LCNEC)). Paraganglioma is added for the completion of NETs classification. Carcinomas with NE features and NE differentiation are also encountered in the GU tract, particularly in the prostate. Classification of GU NETs is listed in Table 1.

This review highlights the epidemiological data, clinical information, histopathological features, prognostic factors, therapeutic approaches, molecular alterations, and targeted treatments of NETs of the GU tract.

2. Materials and methods

This paper is primarily based on the personal experiences of the co-authors. A PubMed review of the literature was also performed using different combinations of the following keywords “GU tract, renal, urinary bladder, urothelial, prostatic, testicular, NEC, NET, and paraganglioma.” Articles published between January 2008 and January 2019,with the desired keywords in the title or abstract, were included. Also, selected key studies with publication date earlier than 2008 were included. Articles published in any language other than English, animal studies, and articles that did not have the full text available were excluded. Studies of NET or NEC of other organs, studies mainly focusing on other GU tumor types, and papers for which the PubMed manuscript link was not accessible were withdrawn.

3. Results and discussion

a. Neuroendocrine tumors (NETs) of the prostate

The prostate gland is the most common site of extrapulmonary NETs [1,2]. NE differentiation in prostate cancer is rare at initial diagnosis but becomes more common after androgen deprivation therapy. The development of NE features correlates with advanced disease,

Abbreviations: AR, androgen receptor; CT, computed tomography; EGFR, epidermal growth factor receptor; EMA, epithelial membrane antigen; GU, genitourinary; LCNEC, large-cell neuroendocrine carcinoma; MEN, multiple endocrine neoplasia; MRI, magnetic resonance imaging; NE, neuroendocrine; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; NSE, neuron-specific enolase; PAP, prostatic acid phosphatase; PNET, primitive neuroectodermal tumor; PSA, prostate-specific antigen; SCNEC, small-cell neuroendocrine carcinoma; SDHB, succinate dehydrogenase B; TTF-1, thyroid transcription factor; TURBT, transurethral resection of bladder tumor; VHL, Von Hippel-Lindau; WDNET, well-differentiated neuroendocrine tumor; WHO, World Health Organization

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Table 1

Prostate	Urinary bladder	Kidney and renal pelvis
Well-differentiated neuroendocrine tumor (carcinoid) Neuroendocrine differentiation in prostatic adenocarcinoma Small-cell neuroendocrine carcinoma Large-cell neuroendocrine carcinoma	Well-differentiated neuroendocrine tumor Small-cell neuroendocrine carcinoma Large-cell neuroendocrine carcinoma	Well-differentiated neuroendocrine tumor Small-cell neuroendocrine carcinoma Large-cell neuroendocrine carcinoma

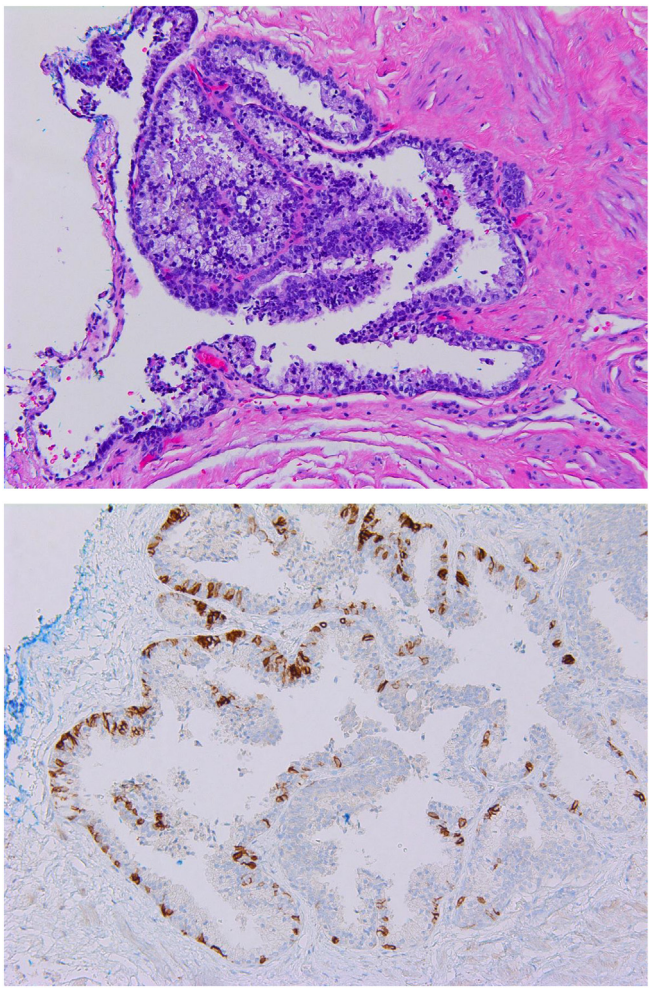

Fig. 1. NE cells dispersed in the acini and ducts of the normal prostate gland seen only by immunohistochemical staining for commonly used NE markers (chromogranin in this case).

refractoriness to currently available therapies, and poor outcomes. The WHO classification includes five categories of prostate cancer types with NE differentiation, namely: NE cells in typical prostate adenocarcinoma, adenocarcinoma with Paneth cell-like NE differentiation, WDNET, SCNEC, and LCNEC [3,4]. NE cells are normally seen dispersed in the acini and ducts of the normal prostate gland on immunohistochemical staining for commonly-used NE markers (Fig. 1) (synaptophysin, chromogranin A, neuron-specific enolase (NSE), and CD56) in addition to bioactive hormones such as serotonin and somatostatin [5]. The majority of NE tumors in the prostate arise from transdifferentiation from typical prostatic adenocarcinoma, with a small fraction of cases arising directly from prostatic stem cells, benign luminal cells, or NE cells [6].

The molecular events leading to NE tumors arising from prostatic stem cells, benign luminal cells, or native NE cells are poorly understood. Conversely, several molecular alterations have been studied and found to be implicated in the NE differentiation of typical prostatic adenocarcinoma cells. AURKA (aurora kinase A) and MYCN gene amplification in typical prostatic adenocarcinoma was associated with the development of NE features later in the disease course [5-7]. Other genetic alterations that were seen more frequently with NE morphology include the loss of Rb (retinoblastoma), TP53, and PTEN genes, and down-regulation or loss of the REST (RE1-silencing transcription factor) gene [6-8]. ERG gene fusion with one of the androgen-regulated genes (TMPRSS2, SLC45A3, and NDRG1) was encountered in around 50% of SCNEC cases. This gene fusion, in conjunction with androgen receptor (AR) gene amplification, was found to downregulate the ERG gene and lead to NE differentiation of typical adenocarcinoma cells [6,7]. Deletion of both the MAP3K7 and CHD1 genes has been shown to cause aggressive (including NE) differentiation of prostatic adenocarcinoma cells [9]. Most of the aforementioned molecular changes were found to be shared by adenocarcinoma with NE differentiation, LCNEC, and SCNEC in the prostate, which led several authors to believe that these entities are on a continuum of differentiation from epithelial to NE cells, with large NE cells representing an intermediate between adenocarcinoma and SCNEC [6] . More interestingly, they showed that a single tumor could have the three components simultaneously, either admixed together or with distinct boundaries between the different components [6].

i. Well-differentiated neuroendocrine tumors (WDNETs/carcinoid)

Primary WDNET of the prostate, also known as carcinoid tumor, is extremely rare, with few individual case reports in the literature [10-13]. The rarity of cases does not allow for an accurate description of age distribution and prognostic outcomes. The few described cases were either diagnosed incidentally or had advanced or symptomatic disease. Common symptoms include hematuria, frequency, and dysuria [11,14,15]. Grossly, these tumors can vary from small, discrete masses to large masses that infiltrate the entire prostate [15]. On histologic examination, the typical morphology of carcinoid tumors in usual sites (lung or GI tract) is seen in prostatic carcinoid tumors: organoid growth pattern and polygonal or spindled cells with low-grade nuclear features (Fig. 2). As most of the cases that are thought to be carcinoid tumors are actually prostatic adenocarcinoma with NE features, associated prostatic adenocarcinoma must be ruled out before rendering a diagnosis of primary prostatic carcinoid tumor. Essential to drawing that distinction is the lack of staining of carcinoid tumor cells with prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) [7,14,15].

ii. Neuroendocrine (NE) differentiation in prostatic adenocarcinoma

Some degree of NE differentiation is seen in almost all cases of prostatic adenocarcinoma, including primary untreated prostatic adenocarcinoma (i.e., hormone naïve) and prostatic adenocarcinoma treated with androgen deprivation. Clusters or scattered single NE cells cannot be differentiated from typical prostatic adenocarcinoma cells on H&*E*-stained sections and are demonstrated only by the use of NE markers (Fig. 3) [2,15-17]. Genetic alterations detected in prostatic adenocarcinoma cells with expression of NE markers suggest that they are indeed malignant cells that underwent NE differentiation. Moreover, these cells expressed PSA, suggesting a common progenitor between these cells and typical prostatic adenocarcinoma cells. The role of NE cells in the development, progression, and the overall prognosis of

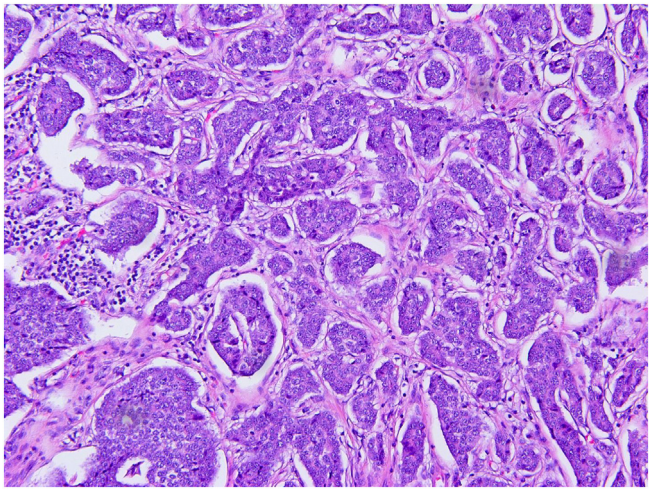

Fig. 2. Prostatic carcinoid tumor with typical morphology of carcinoid tumors seen elsewhere, with organoid growth pattern and polygonal cells with low-grade nuclear features.

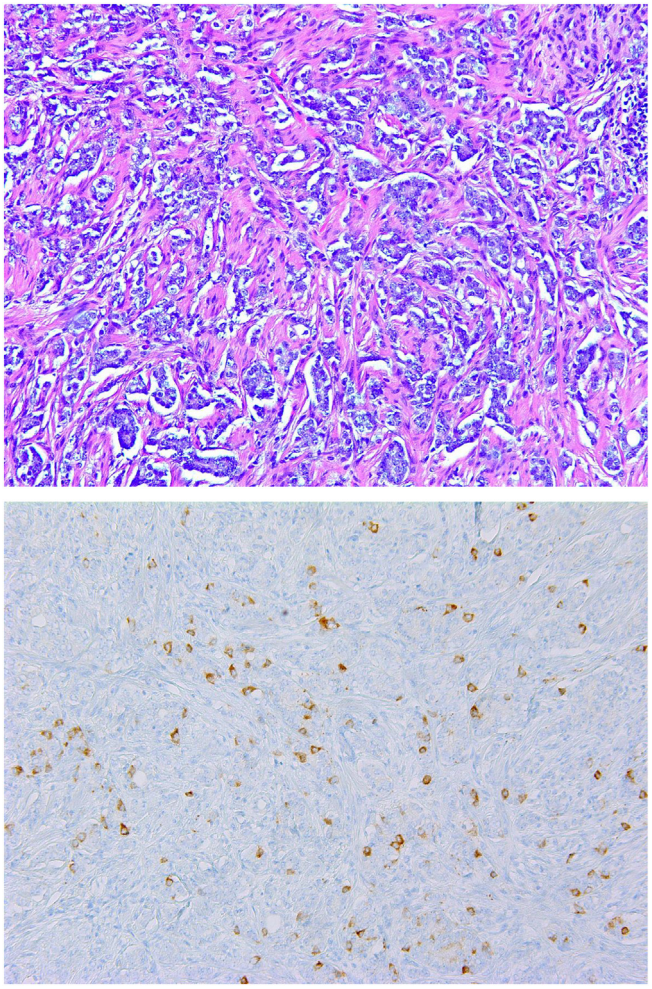

Fig 3. Some degree of NE differentiation is seen in almost all cases of prostatic adenocarcinoma. Clusters or scattered single NE cells in prostatic adenocarcinoma are shown by the staining with chromagranin.

prostatic adenocarcinoma is controversial. Reduced or complete lack of expression of AR in NE cells and the increased number of NE cells seen in association with decreased androgen sensitivity led to the hypothesis that they play a role in conferring androgen insensitivity to typical

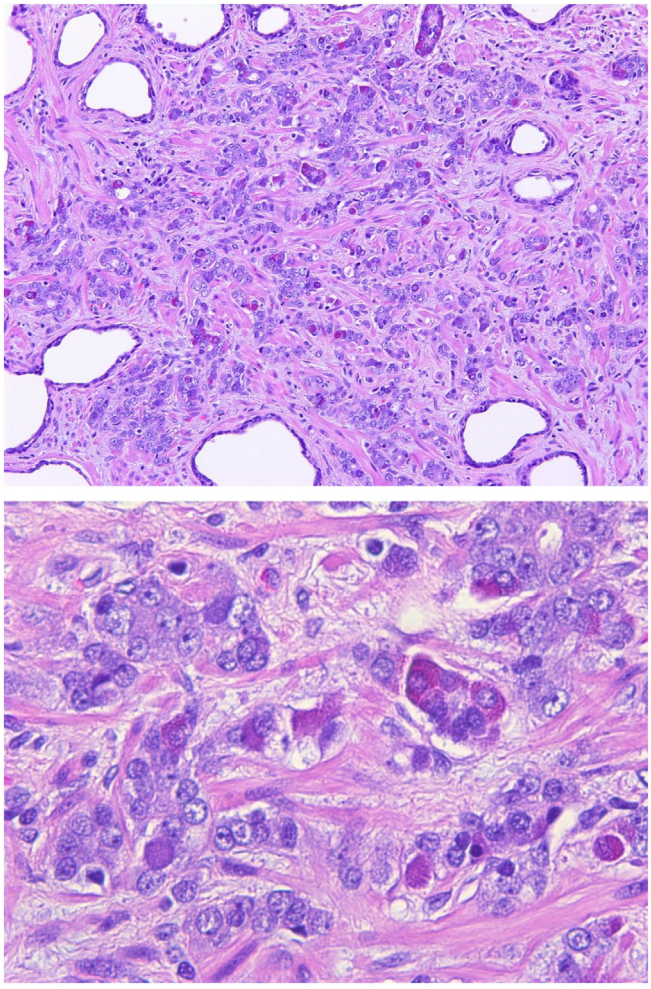

Fig. 4. Prostatic adenocarcinoma with Paneth cell-like differentiation contains cells with eosinophilic cytoplasmic granules that are positive for NE markers admixed with typical prostatic adenocarcinoma cells. Unlike typical prostatic adenocarcinoma, the Paneth cell-like variant has small nuclei with speckled chromatin and absent to inconspicuous nucleoli.

prostatic adenocarcinoma. Also, it has been suggested that NE cells affect the surrounding tumor cells by altering the tumor microenvironment through paracrine secretions [5-7,16,18]. However, the prognostic significance of detecting and quantifying NE differentiation in prostatic adenocarcinoma is debatable. Most studies investigating the prognostic value of NE differentiation in typical prostatic adenocarcinomas have shown that the grade and stage are the main determinants of prognosis and that NE differentiation is not an independent risk factor for worse prognosis [5-7,16]. Therefore, we do not recommend the routine use of NE markers in otherwise typical prostatic adenocarcinomas.

A small subset of prostatic adenocarcinoma shows Paneth cell-like differentiation, with eosinophilic cytoplasmic granules that are positive for NE markers admixed with typical prostatic adenocarcinoma cells. Unlike typical prostatic adenocarcinoma, the Paneth cell-like variant has small nuclei with speckled chromatin and absent to inconspicuous nucleoli (Fig. 4). It is important to recognize this variant, as it can grow in solid nests or cords rather than glands, and can cause unwarranted upgrading to Gleason pattern 4 or 5, leading to more aggressive management. It has been shown that the overall outcome of prostatic adenocarcinomas with Paneth cell-like change is solely dependent on the stage and grade of the typical adenocarcinoma areas. Based on this, Paneth cell-like areas of the tumor should not be included in the Gleason grade [2,6]. Another variant of Paneth cell-like change that

lacks the typical eosinophilic granules has been described. This variant can be harder to distinguish from the typical prostatic adenocarcinoma cells. However, the lack of prominent nucleoli, classically seen with typical prostatic adenocarcinoma, and the focal presence of more typical Paneth cell-like cells with retained eosinophilic granules, are useful clues to this variant. The use of NE markers is advocated in this scenario to avoid unwarranted upgrading [19].

iii. Small-cell neuroendocrine carcinoma (SCNEC)

Primary SCNEC accounts for 1–5% of all prostatic malignancies. Patients can either develop SCNEC de novo or, more commonly, after androgen deprivation therapy for typical prostatic adenocarcinoma [7,12,15]. Regardless of the origin of the SCNEC of the prostate, it is an aggressive form of cancer, with poor prognosis [20]. SCNEC and typical adenocarcinoma have similar clinical pictures. Some clinical features that favor SCNEC include: i) rapidly progressive urinary symptoms; ii) advanced metastatic disease at presentation with low serum PSA level and unusual sites of metastases; iii) resistance to androgen deprivation therapy; iv) detection of serum NE markers (chromogranin A and NSE) on diagnosis or in the course of the disease; and v) the presence of predominantly osteolytic metastatic lesions, rather than the osteoblastic lesions classically seen with typical adenocarcinoma [2]. In addition, development of paraneoplastic syndromes, like Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion, Eaton-Lambert syndrome, limbic encephalitis, and peripheral neuropathy, have been reported with SCNEC of the prostate more frequently than in typical prostatic adenocarcinoma [14,21-23]. Histologically, SCNEC of the prostate is similar to SCNEC of other sites, with infiltrative, solid, or nested arrangement of small cells (typically < 3 resting lymphocytes), with scant cytoplasm and high nuclear-cytoplasmic ratio, nuclear molding, and fine chromatin with absent or inconspicuous nucleoli. Frequent mitoses, a high Ki-67 proliferation index, and scattered single-cell necrosis or large areas of necrosis are typically seen (Fig. 5) [12,15]. Pure SCNEC should not be assigned a Gleason score, and in cases where it is mixed with typical adenocarcinoma, the SCNEC component should be excluded from the grading process [6,15]. Immunohistochemically, these tumors can either express the conventional NE markers (synaptophysin and chromogranin A), with or without CD56 expression, or have complete lack of expression of any NE marker in about 10% of cases [14,24]. Insulinoma associated protein 1 (INSM1) is a recently developed NE tumor marker that proved to be highly sensitive and specific to detect SCNEC of the prostate [25]. For metastatic lesions, it is important to rule out a primary pulmonary SCNEC; however, thyroid transcription factor (TTF-1) cannot be used to confidently differentiate the two entities as it was found to be expressed in > 50% of prostatic primary SCNEC in some studies [15,26]. Other studies have found it to be expressed in smaller proportion of cases [14]. Less than 20% of SCNEC of prostatic origin retain PSA positivity, and in these cases, PSA immunostaining can confirm a prostatic primary of a metastatic SCNEC [6,7]. Prostatic SCNEC can be hard to differentiate from high-grade prostatic adenocarcinoma, particularly on needle core biopsies or in specimens with crush artifact. In this case, NE marker positivity and negative or patchy weak staining with PSA and PAP can be used as unequivocal evidence for SCNEC (Fig. 6). Also, strong and diffuse PSA and PAP expression advocates against prostatic SCNEC. Moreover, cyclin D1 loss has been found to correlate with NE differentiation and was suggested as one of the markers to be used in the differentiation between SCNEC and high-grade prostatic adenocarcinoma [27]. Despite multimodal management, with surgery, platinum-based chemotherapy, and radiation, the mean survival is less than a year after diagnosis [28]. Targeted therapies are being investigated, but none are currently available [7,16].

iv. Large-cell neuroendocrine carcinoma (LCNEC)

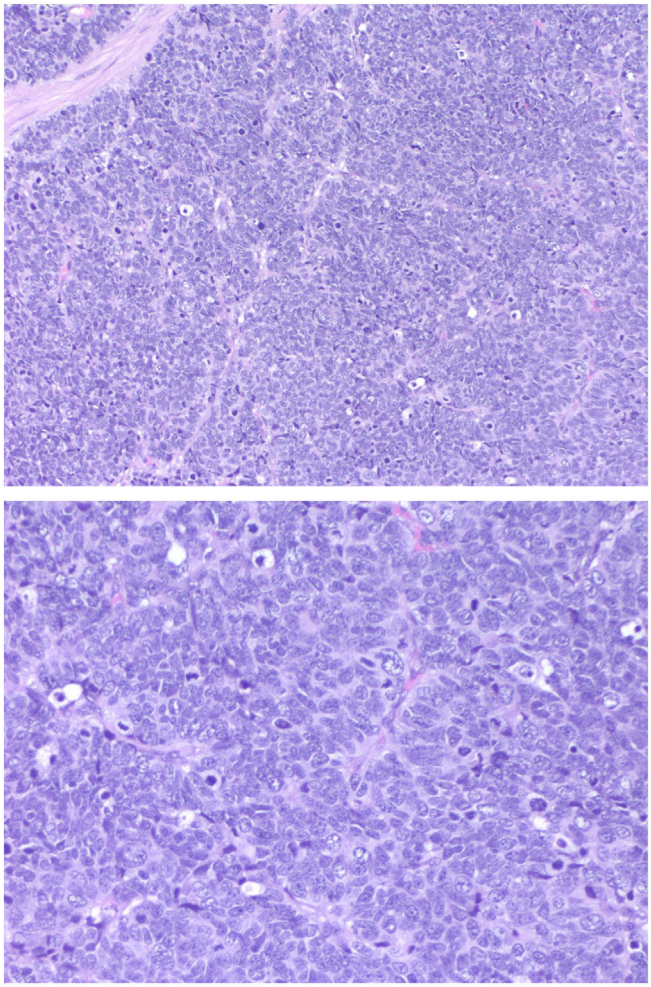

Fig. 5. SCNEC of the prostate with infiltrative, solid arrangement of small cells, with scant cytoplasm and high nuclear-cytoplasmic ratio, nuclear molding, and fine chromatin with absent or inconspicuous nucleoli; frequent mitoses are observed.

LCNEC of the prostate is extremely rare, particularly in its pure form, with only a few cases reported in the literature [3,29]. Histologically, it resembles LCNEC in other organs, with neoplastic cells that are larger than cells of typical prostatic adenocarcinoma or SCNEC, containing abundant amphophilic cytoplasm, high nuclear grade with prominent nucleoli, brisk mitotic activity (> 10 per ten high-power fields), and large areas of necrosis. Different growth patterns have been described in these tumors, including nested, trabecular, and rosettoid patterns (Fig. 7). Positivity for at least one of the NE immunohistochemical markers, other than NSE, is needed for the diagnosis. These tumors show either negative staining or patchy positivity with PSA and PAP, and these markers should not be solely used to rule out prostatic origin of metastatic LCNEC [7,29,30]. In some cases, distinguishing between LCNEC and adenocarcinoma with Gleason pattern 5 can be challenging [14]. The reported cases of prostatic LCNEC had a prognosis comparable to that of SCNEC, with early metastasis and rapid deterioration [29,30].

b. Neuroendocrine tumors (NETs) of the urinary bladder

NETs of the urinary bladder are classified into WDNET, SCNEC, and LCNEC, in addition to paraganglioma [3]. The cell of origin of these tumors remains uncertain. NE cells found in the basement membrane of normal urothelium and reactive urothelial lesions may give rise to WDNET, while less differentiated NETs seem to arise from divergent

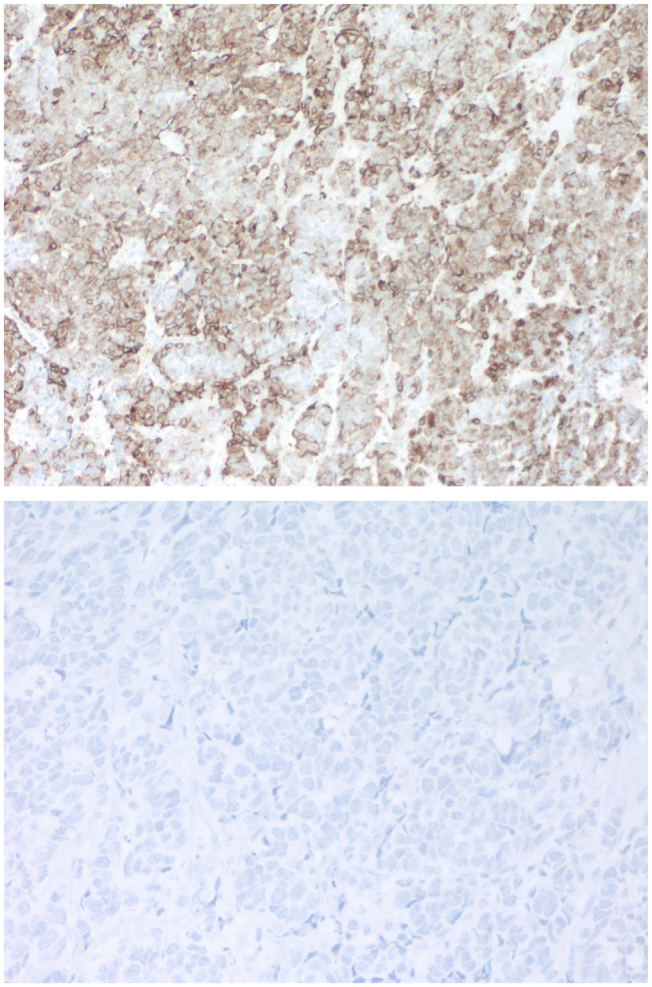

Fig. 6. Positivity for the NE marker chromogranin (top panel) with loss of PSA staining (bottom panel) can be used as unequivocal evidence for SCNEC.

differentiation of urothelial carcinoma [31].

i. Well-differentiated Neuroendocrine Tumors (WDNETs)

WDNETs of the urothelium and urinary bladder are extremely rare, with < 25 cases described in the literature [14]. Using the term "carcinoid tumors" to describe these lesions is discouraged in the most recent WHO classification [3]. Based on the few described cases in the literature, patient demographics are similar to those of urothelial carcinoma. These tumors typically arise in middle-aged to elderly men who are usually asymptomatic; the tumors are found incidentally on cystoscopy done for other reasons. Conversely, patients may present with nonspecific symptoms of hematuria and irritative urologic symptoms, or with obstructive symptoms, if the tumor is located in the urethra. Carcinoid syndrome has not been reported in association with urinary bladder WDNET [32].

Grossly, these lesions mostly consist of small (< 3 cm) nodules or polyps, located in the bladder neck or trigone area. Histologically, these tumors are usually located in the lamina propria and show the typical pattern of carcinoid tumors in other locations, with trabecular, pseudoglandular, or acinar architectures with frequent association with cystitis cystica and cystitis glandularis. The neoplastic cells have 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. Staining with NE markers (synaptophysin, chromogranin, and CD56) is

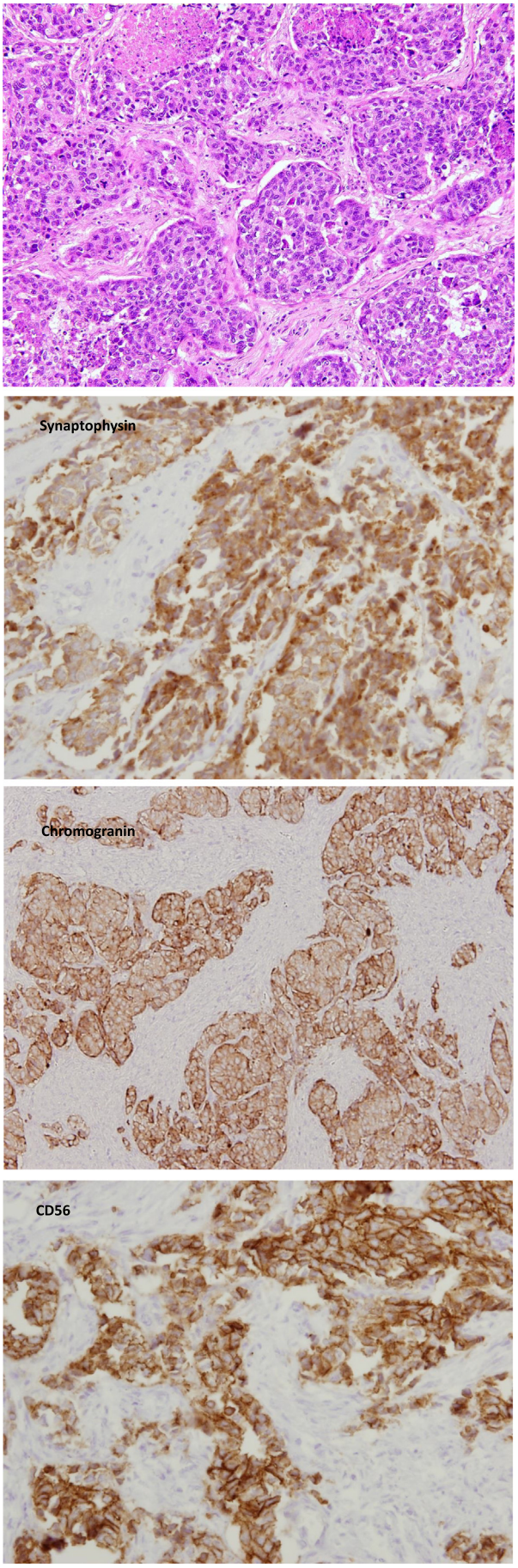

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Fig. 7. LCNEC of the prostate with neoplastic cells that are larger than cells of typical prostatic adenocarcinoma or SCNEC, containing abundant amphophilic cytoplasm, high nuclear grade, brisk mitotic activity, and large areas of necrosis.

seen in these tumors, in addition to occasional PAP positivity, but not other prostate-specific markers [31-33]. In the few cases where long-term outcomes have been documented, no recurrence or disease progression has been reported [32].

ii. Small-cell neuroendocrine carcinoma (SCNEC)

Previously known as oat cell carcinoma, SCNEC accounts for < 1% of bladder tumors [34], but it is more common than WDNET and LCNEC, with around 500 new cases per year [31]. These tumors are thought to arise from divergent differentiation of multipotent stem cells in the urothelial lining. This theory is supported by the fact that pure SCNEC of the urinary bladder is exceedingly rare, and these tumors are usually found in association with either urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, or sarcomatoid carcinoma [34-37]. A large series of 51 patients with SCNEC of the urinary bladder showed that the majority of the cases had a urothelial carcinoma, and less commonly adenocarcinoma or squamous cell carcinoma, components with only 12% having SCNEC without other components [38]. Additional studies that demonstrated a common clonal origin of coexisting urothelial carcinoma and SCNEC further substantiate this claim [31]. Although bladder SCNEC tends to have a better prognosis than SCNEC of the prostate [14], NE differentiation of urothelial carcinoma confers a worse prognosis, with more early distant metastasis than typical urothelial carcinoma [39,40].

SCNEC typically affects older males with a history of smoking. Hematuria is the most common presenting symptom, and irritative and obstructive symptoms are less commonly seen [34]. Features of paraneoplastic syndrome, in the form of humoral hypercalcemia of malignancy secondary to the production of parathyroid hormone-related protein, can be seen in such cases [21].

On macroscopic and cystoscopic examination, SCNEC can originate from anywhere in the bladder, including the urachus, and has similar features to urothelial carcinoma, with polypoid, nodular, or ulcerated appearance, and variable degrees of muscular and perivesical fat invasion [14,34,41]. Histological examination shows the classical features of SCNEC in other organs, with overlapping, small, round to oval, hyperchromatic nuclei with nuclear molding, speckled or “salt and pepper” chromatin pattern, no or inconspicuous nucleoli, scant cytoplasm, a high mitotic rate (> 10 mitoses/10 high-power fields), and necrosis [34,39]. SCNEC of the urinary bladder typically expresses markers of epithelial and NE differentiation. A panel of NSE, CD56, synaptophysin, and chromogranin A is typically used to demonstrate NE differentiation. These NE markers are not always expressed in such tumors, and the diagnosis can be based solely on examination of hematoxylin and eosin stained sections [3,34,35,39]. 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 [3,34,42]. Detection of expression of somatostatin receptors (SSTRs) type 2A and type 4 in SCNEC of the urinary bladder has been documented [43]. Varying rates of positivity for P53, P16, epidermal growth factor receptor (EGFR), and c-Kit immunohistochemical staining has been documented in different case reports and case series. Epithelial markers, like CK7 and epithelial membrane antigen (EMA), are usually positive [34-37,39,40]. CK20, which is commonly positive in urothelial carcinoma, is usually negative in SCNEC [31]. Differentiating between primary SCNEC of the urinary bladder and SCNEC arising in the prostate and involving the bladder has important clinical implications. PSA and PAP expression can be lost in prostatic SCNEC, but not in the more differentiated prostatic adenocarcinoma components. Thus, PSA and PAP staining can be a valuable differentiation tool [31,44]. Also, HOXB13 (homeobox B13) is a specific and sensitive prostate marker that can be used, especially in poorly differentiated NETs [45].

Chemotherapy with or without radiation is the mainstay of treatment in SCNEC of the urinary bladder, but unlike SCNEC of the lung, surgical management has an important role [34,46-50]. 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 [51-53].

iii. Large-cell neuroendocrine carcinoma (LCNEC)

LCNEC of the urinary bladder is rare, with < 30 cases reported in the literature [54]. These tumors have a predilection to older males, and generally have aggressive biological behavior and dismal prognosis; pure forms have a worse prognosis than mixed histology [31,54,55]. Imaging studies including contrast-enhanced CT and PET/CT scans are used in staging and in localizing distant metastasis, but octreotide scanning, commonly used in more differentiated NETs, is not useful in these cases [46].

The cells giving rise to this type of tumor are thought to be the same cells giving rise to SCNEC [31,35]. Similar to LCNEC in the lung, microscopic examination of LCNEC of the urinary bladder shows large, polygonal cells, low nuclear-cytoplasmic ratio, polymorphic nuclei, coarse chromatin, and prominent nucleoli [56]. Mitoses and necrosis are more pronounced than in SCNEC [31]. Mixed histology with LCNEC and urothelial, squamous, adenocarcinoma, or sarcomatoid carcinoma is commonly encountered [48]. Like other tumors with NE features, synaptophysin, chromogranin A, CD56, and NSE are usually positive in these tumors, along with epithelial markers like CK AE1/AE3, CAM 5.2, and EMA. The exceptionally high Ki-67 index in LCNEC (> 95% in some cases), along with positive staining with NE markers, serves to confidently distinguish this entity from urothelial carcinoma [56,57]. Unlike SCNEC, LCNEC of the urinary bladder showed no TTF-1 positivity in the reported cases [56]. Of note, chromogranin A is less sensitive in LCNEC than in SCNEC in the urinary bladder [31]. Given the rarity of this tumor, treatment plans are based on extrapolation from the literature on pulmonary LCNEC [55]. A single case of primary LCNEC of the ureter has been reported. It showed pure LCNEC morphology, and stained with NE markers and cytokeratin, but not with uroplakin or TTF-1 [58].

c. Neuroendocrine tumors (NETs) of the kidney and renal pelvis

Primary renal cell carcinomas with NE differentiation have been reported in the literature in recent years, most notably chromophobe renal cell carcinoma, and less commonly in other types like mucinous tubular and spindle cell carcinoma [59-62]. NE cells are not normally found in the kidney parenchyma and pelvis, and the cell of origin of NETs in these locations is thought to be multipotent stem cells that show NE differentiation [15,61]. The WHO histologic classification of NETs of the kidney spans a spectrum from WDNETs to high-grade NECs (SCNEC and LCNEC) [3].

i. Well-differentiated Neuroendocrine Tumors (WDNETs)

WDNETs of the kidney, also known as carcinoid tumors, are very rare, with around 90 cases reported in the literature. Worth noting is the considerable correlation between WDNETs and congenital or acquired renal anomalies, with up to 26% of renal carcinoids occurring in horseshoe kidneys. In addition, 15% of renal WDNETs arise in mature renal teratomas [63-68]. Patients are typically younger than renal cell carcinoma patients, and are either asymptomatic or present with nonspecific symptoms such as hematuria, abdominal mass, or fever. Hormonally-active renal WDNETs are seen in < 15% of the reported cases. Carcinoid syndrome (flushing, diarrhea, abdominal pain, generalized

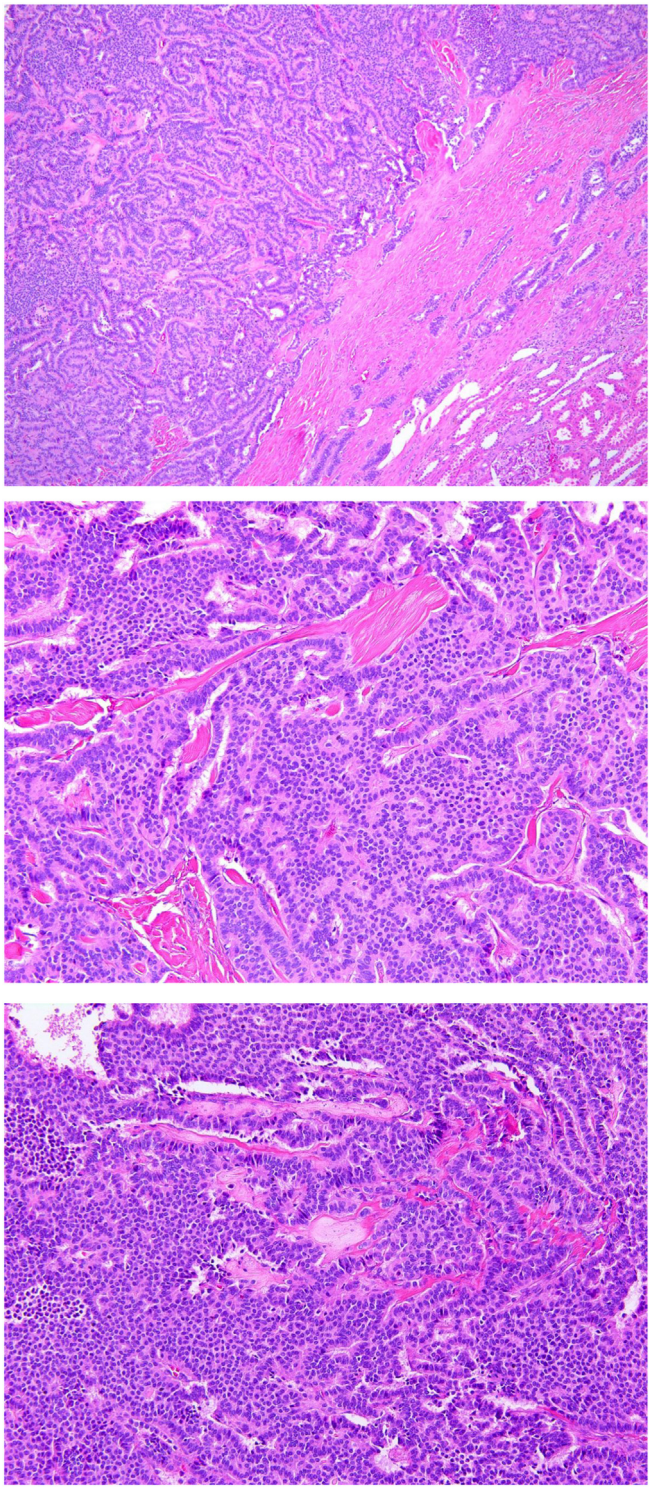

Fig. 8. Renal WDNET (carcinoid tumor) with trabecular growth pattern. The tumor cells are monotonous, small, and round with eosinophilic cytoplasm and low mitotic count.

edema, and bronchoconstriction), with the detection of 5-hydroxyindoleacetic acid in the urine secondary to serotonin release, is more common than VIPoma, Cushing syndrome, glucagonoma, and insulinoma [69,70]. Somatostatin receptor imaging using octreotide helps in identifying metastasis and in detecting recurrence [71,72]. Similar to other retroperitoneal tumors, WDNETs can grow up to 17 cm in diameter, with 75% of patients presenting with tumors larger than 4 cm; around half of patients present with extrarenal extension or distant metastasis [71].

Grossly, these tumors are usually solitary, well-demarcated from the surrounding kidney parenchyma, with heterogeneous solid and cystic cut surface and focal calcification. Histologically, WDNETs of the kidney can show different growth patterns including solid sheets, solid nests, and glandular, with trabecular growth pattern being the most commonly encountered (Fig. 8). Tumor cells are monotonous, small, and round, with eosinophilic cytoplasm, a low mitotic count, and a low Ki-67 proliferation index. The distinctive morphology leads to the correct diagnosis in most cases. In some instances, confusion with other renal tumors, like oncocytoma, clear cell or papillary renal cell carcinoma, primitive neuroectodermal tumor (PNET), and metanephric adenoma can occur, necessitating further analysis.

Renal WDNETs are usually positive for NE markers and cytokeratin. Unlike renal cell carcinoma and PNET, which show consistent positivity for PAX-8 and CD99, respectively, WDNETs are rarely positive for these markers [66,67,70,72-75]. Management of these tumors is mainly with surgical excision, with no documented survival benefit of chemotherapy and radiation [70]. A case of renal carcinoid with vascular endothelial growth factor activation has been reported, opening the door for anti-angiogenic therapy as a potential treatment option in such cases [76]. Renal WDNETs have variable outcomes, with age at presentation (> 40 years), size (> 4 cm), extrarenal extension, purely solid cut surface, and > 1 mitoses per high-power field appearing to be the most important prognostic factors. Interestingly, tumors arising in horseshoe kidneys or mature teratomas appear to have a better prognosis even with metastasis [70,71,73]. WDNETs can arise in the renal pelvis and calyces, but those are exceptionally rare, with only four cases reported in the literature [63].

ii. High-grade neuroendocrine tumors (NETs)

Similar to SCNECs in other sites, primary renal SCNEC is a high-grade tumor with poor prognosis. On average, it is seen in patients who are older than those with renal WDNETs. Around 75% of patients die of their disease within a year from the diagnosis. These tumors are extremely rare in the kidney, with approximately 50 cases reported in the literature. The average age at presentation is 59 years and there is no sex predilection. The most common symptoms are hematuria, abdominal pain, and weight loss. Computed tomography (CT) scanning and magnetic resonance imaging (MRI) studies are not useful in differentiating between SCNEC and other epithelial tumors of the kidney [1,15,71,77,78]. On gross examination, the tumor typically shows an ill-defined border and a soft and friable cut surface with necrosis. Invasion of the renal sinus, renal vein, and perirenal fat is common. Histologic examination shows the same histologic feature of SCNEC of other organs: a solid or nested growth pattern of cells with small, round, and hyperchromatic nuclei, with nuclear molding, dispersed chromatin, and inconspicuous nucleoli. Brisk mitotic activity and necrosis are almost always encountered, and Azzopardi phenomenon is frequently seen in SCNECs. Immunohistochemically, these tumors show positivity for NE markers, variable staining with cytokeratin stains, and negative staining with TTF-1, which helps to exclude metastatic lung SCNEC. Lymph node and distant metastasis are commonly seen on presentation. Fluorescence in-situ hybridization performed on one case of SCNEC of the kidney showed a gain of multiple chromosomes, loss of the P53 gene, and MYC gene amplification. This pattern of chromosomal aberration is different from the pattern seen in clear cell renal cell carcinoma, which is characterized by chromosomal loss, especially the short arm of chromosome 3 (3p). This suggests different origins of renal SCNEC and other more common renal tumors [79].

Unlike SCNEC arising in the renal parenchyma, which more often has pure NE differentiation, SCNEC arising in the renal pelvis is associated with urothelial or squamous cell carcinoma [1,75,77].

Primary LCNEC of the kidney is extremely rare, with fewer than ten cases reported in the literature. Clinically, they present and behave like

SCNEC. Histologically, the tumors cells are large and have abundant cytoplasm. The nuclei are pleomorphic, with vesicular chromatin, prominent nucleoli, and cells have a high mitotic rate (> 10/10 high-power fields). Large areas of necrosis are commonly seen. Due to the poorly differentiated nature of this tumor, high-grade renal cell and urothelial carcinomas have to be ruled out before rendering a diagnosis of LCNEC. This can be achieved by establishing NE differentiation by at least focal positivity with an NE marker [15,79-81].

d. Neuroendocrine tumors (NETs) of the testis

i. Testicular carcinoid tumors

Primary testicular carcinoid tumors represent < 1% of all testicular tumors. The clinical presentation is commonly a testicular mass or swelling in middle-aged men with absence of pain or symptoms of carcinoid syndrome [82-84]. Testicular carcinoid tumors are postulated to arise from teratomas or other germ cell tumors of the testis. This notion is supported by the presence of a teratomatous component in up to 25% of the reported cases and by the multipotent nature of germ cells. Furthermore, shared genetic abnormalities, namely isochromosome 12p and 12p overrepresentation, have been demonstrated to exist in carcinoid tumors and in the background teratomas [85,86]. Also, there have been reported cases in which germ cell neoplasia in situ has been seen in testes with carcinoid tumor [15]. Extensive sampling of the tumor and the surrounding normal-appearing testicular parenchyma is encouraged to elucidate the presence of germ cell neoplasms or scars, denoting a regressed or burnt-out germ cell tumor, in cases of primary testicular carcinoids.

Macroscopically, testicular carcinoid tumors are solid, tan to white, round, and well-circumscribed. When germ cell tumors are present, cystic changes, hemorrhage, necrosis, or scarring in the adjacent parenchyma can be seen. Histologically, these tumors have the distinctive look of carcinoid tumors in other sites, with cells having monotonous nuclei, speckled chromatin, and abundant cytoplasm, growing most commonly in a trabecular or insular pattern (Fig. 9). Mitoses are few and necrosis, including comedo type necrosis, can be seen in larger tumors [83,84,87]. Generally, these tumors are of low grade and behave in an indolent fashion and are confined to the testis in 85–90% of the reported cases. Yet, a case with intermediate grade features, leading to death from the disease within a year from diagnosis, was reported. Histologically, this case had haphazard arrangement of the neoplastic cells, comedo-like necrosis, cellular atypia, and up to 8 mitoses per 10 high-power fields [87].

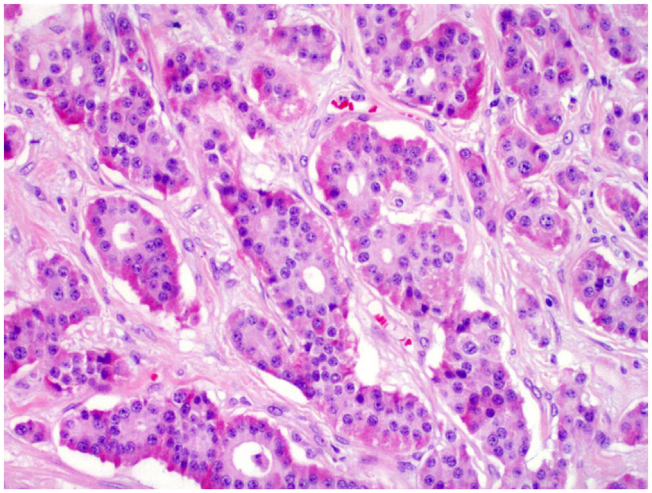

Fig. 9. Testicular carcinoid tumor with insular/trabecular growth pattern. The neoplastic cells have monotonous nuclei, speckled chromatin, and abundant cytoplasm. (courtesy from Dr. Charles Guo, MD Anderson Cancer Center, Houston, TX)

The treatment of choice for testicular carcinoid tumors is orchiectomy. Long-term follow-up and surveillance for recurrence is important, as metastasis can occur sometimes years after the initial presentation and often with more aggressive behavior. Imaging studies with octreotide scanning can help in ruling out metastasis, and in conjunction with the detection of urinary 5-hydroxyindoleacetic acid, can aid in surveillance [15,82]. Other types of primary testicular tumors can show aberrant expression of some NE markers, warranting cautious interpretation of IHC studies. A subset of Sertoli cell tumors can express CD56 [88]. Also, one case of relapsing seminoma with an NE carcinoma component that expressed synaptophysin and chromogranin was reported [89].

e. Other neuroendocrine tumors in the genitourinary tract

Very rare cases of penile SCNEC [14] and scrotal LCNEC have been reported [90].

f. Paraganglioma

Extra-adrenal paraganglioma, also known as extra-adrenal pheochromocytoma, is a relatively rare NET that arises from chromaffin cells in autonomic ganglia. In the GU tract, paraganglioma is most common in the bladder, but it has been reported in the kidney, renal pelvis, ureter, urethra, prostate, spermatic cord, and seminal vesicles [91-99]. About two-thirds of the paragangliomas arising in the GU tract are sporadic, and one-third are seen in association with inherited disorders such as germline mutation in succinate dehydrogenase B (SDHB), von Hippel-Lindau disease (VHL), type 1 neurofibromatosis (NF-1), Carney triad, multiple endocrine neoplasia (MEN) types 2A and 2B, and familial paraganglioma syndrome [91,100-103].

Most paragangliomas are biochemically functional, which necessitates the use of α-blockers to curb the systemic effects of catecholamines prior to surgical resection, which is the mainstay of treatment in GU paragangliomas [100,104-109]. CT and MRI can be used to detect paragangliomas, but both have a lower sensiti0076ity and specificity than radioisotope scanning with ^{131}Iodine metaiodinebenzylguinidine (MIBG) [107-110].

Although the majority of paragangliomas have a good prognosis and are considered benign, malignancy is occasionally seen and is defined by metastasis or extensive local disease. Tumors associated with mutations in SDHB are more likely to show malignant behaviors [29,88,99,101].

i. Paraganglioma of the urinary bladder

Despite being the most common site of paraganglioma in the GU tract, urinary bladder paragangliomas represent < 0.6% of bladder tumors. These tumors present with the classic symptoms of hypertension, hematuria, and micturition syncope in around half of the reported cases, with paroxysmal palpitation and diaphoresis less commonly seen [46,107,109,112,114-118].

The gross appearance of these lesions is of a solitary, well-circumscribed, intravesical exophytic or intramural nodule, no > 2–5 cm in dimension. The ubiquitous nature of paraganglia in the bladder makes staging such tumors a difficult task. Less than 15% of bladder paragangliomas are malignant with extensive local disease, i.e., deep local invasion or invasion of adjacent structures, lymph nodes, or distant metastases [101,111,113,114,119-121].

Histologically, paragangliomas show the characteristic “zellballen” morphology seen in other paragangliomas, with polygonal cells that have finely granular amphophilic cytoplasm and ovoid nuclei embedded in a richly vascularized fibrous stroma (Fig. 10). Nuclear pleomorphism, occasional mitotic figures, and focal neuroblastic or

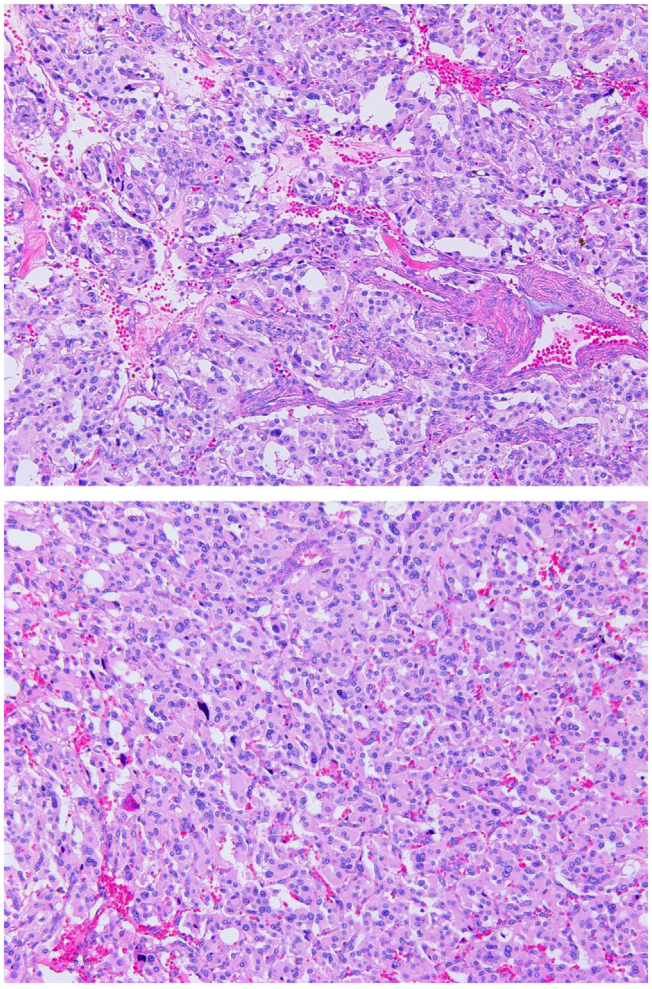

Fig. 10. Urinary bladder paraganglioma with the characteristic "zellballen" morphology. The neoplastic cells are polygonal and have finely granular amphophilic cytoplasm and ovoid nuclei embedded in a richly vascularized fibrous stroma.

ganglioneuromatous differentiation can be seen, but no correlation has been shown between these parameters and the malignant potential of the tumor [46,101,109,114,119,122].

Although the diagnosis of paraganglioma can be readily rendered on hematoxylin and eosin stained sections, immunohistochemical stains may be needed in some cases. Bladder paraganglioma can have a histological resemblance to nested variant of urothelial carcinomas or urothelial carcinoma with NE 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. In such instances, cytokeratin and P63 positivity rule out paraganglioma. On the other hand, GATA3, which is classically known as a urothelial marker, is positive in up to 89% of paraganglioma cases. This poses a potential pitfall of misdiagnosing paraganglioma as urothelial carcinoma based on GATA3 positivity [121, 123 (p3), 124 (p3), 125-127].

Like other tumors of NE origin, synaptophysin, chromogranin A, 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 and melanoma [101]. The use of SDHB immunostains can be used to predict biological behavior and screen cases, and subsequent mutational analysis can be performed on cases that show loss of staining [95,111].

4. Conclusion

Primary NETs in the GU tract are much rarer than in the lung or the GI tract. This warrants diligent search for primaries outside the GU tract before rendering such diagnoses. Thus, collaboration between the pathologist and the urologist is essential. Despite the advances in imaging techniques, serum marker studies, and molecular diagnostics, the diagnosis of these tumors continues to be challenging. The use of NE immunohistochemical markers can be a sensitive tool to detect NE differentiation, but not necessarily a specific one. The outcome of these tumors varies, with paragangliomas and WDNETs having a better prognosis than high-grade NETs (SCNEC and LCNEC). Due to the rarity of these cases, no treatment guidelines are available, and patients are usually managed using regimens extrapolated from NE tumors at other sites.

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