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Original contribution

Well-differentiated neuroendocrine tumors of the lower urinary tract: biologic behavior of a rare entity☆

Maria Del Carmen Rodriguez Pena MD[a,b], Daniela C. Salles MD[a], Jonathan I. Epstein MD[a], Sofia Canete-Portillo MD[b], Aline C. Tregnago MD[a], July Ramirez MD[a], Abdelrazak Meliti MD[a], George J. Netto MD[a,b,*]

[a] Department of Pathology, Johns Hopkins Hospital, Baltimore, MD, 21287, USA
[b] Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35233, USA

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Summary The spectrum of neuroendocrine (NE) tumors in the genitourinary tract ranges from the aggressive large and small cell carcinomas to the often benign paraganglioma and well-differentiated neuroendocrine tumor (WD-NET). At least 15 pure lower urinary tract (LUT) WD-NETs have been described. Owing to the rarity of WD-NET in the LUT and the limited number of reported cases, a better definition of their biologic long-term behavior is warranted. Herein, we aim to describe 10 new cases of WD-NET arising in the LUT and expand on follow-up findings. Ten consultation cases were identified and included 6 men and 4 women who ranged from 45 to 73 years of age. Seven cases arose in the bladder with one located in the bladder neck, 1 arose in the prostatic urethra, 1 arose in the female urethra, and 1 arose in the left ureteral orifice. All lesions were confined to the lamina propria, and tumor architecture was pseudoglandular in all cases. Associated cystitis cystica et glandularis was identified in 5 cases; urothelial papilloma and florid von Brunn's nests were found in 2 additional cases. Immunohistochemical staining for synaptophysin and chromogranin was diffusely positive in 9 cases and focal in 1 case, and the Ki-67 proliferation index was 5% or less in all tumors. Follow-up ranged from 37 to 137 months (mean = 82; median = 77), and there was no evidence of residual disease or recurrence in any of the 10 patients during the follow-up period.

☆ Disclosures: None.

* Corresponding author. Department of Pathology, The University of Alabama at Birmingham, WP Building, Suite P230, 619 19th Street South Birmingham, AL, 35249-7331, USA.
E-mail address: gnetto@uabmc.edu (G.J. Netto).

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1. Introduction

The most common locations for neuroendocrine (NE) tumors include the gastrointestinal tract and lungs; however, NE tumors can appear at any site [1]. The spectrum of NE tumors in the genitourinary tract ranges from the aggressive large and small cell carcinomas to the often benign paraganglioma and well-differentiated neuroendocrine tumor (WD-NET) [1−3]. NE tumors comprise 1% of all urinary bladder malignancies [4]. Small cell carcinoma accounts for 0.5−1% of the annually estimated 500 NE bladder tumors, whereas paragangliomas represent less than 0.5% [2,4]. The least common NE tumors are large cell NE carcinoma with only few documented case reports [5] and WD-NET. Approximately 20 cases of WD-NETs arising in the lower urinary tract (LUT) have been described in the English literature, of which at least 15 are pure primary bladder or prostatic urethra WD-NETs [4,6,7]. In the 2016 World Health Organization tumor classification of the urinary system and male genital organs, the terminology of carcinoid as a synonym for WD-NET was discouraged (WHO 2016).

WD-NETs are more frequently located in the bladder trigone or neck regions, presenting as a nodular/polypoid mass measuring less than 1 cm with associated hematuria [8]. They exhibit microscopic features identified in WD-NET of other sites including monotonous cells with round nuclei, stippled *salt and pepper* granular chromatin, and eosinophilic cytoplasm arranged in nested, pseudoglandular, or trabecular patterns [5]. Surgical resection remains the gold standard of therapy [4,9]. The cellular origin of WD-NET in the LUT remains uncertain. Hypotheses include tumor derivation from metaplastic bladder urothelium, and NE cells present in reactive lesions or multipotent stem cells [2,3]. A unique feature of LUT WD-NETs is the presence of eosinophilic Paneth-like cytoplasmic basally located granules [6].

Owing to the rarity of WD-NET in the LUT and limited number of hitherto reported cases, a better definition of their biologic long-term behavior is warranted. The average previously published collective follow-up length is 21 months [6,10−17]. Herein, we aim to describe 10 new cases of WD-NET arising in the LUT and expand on follow-up findings.

2. Materials and methods

After Institutional Review Board approval, the surgical pathology electronic medical record database at the Johns Hopkins Hospital (JHH) was searched between 1984 and 2016 for all *carcinoid* and *NE* tumors of the LUT, including consultation cases. Clinical data and postoperative follow-up was obtained for each case. Hematoxylin and eosin−-stained and immunohistochemically stained slides, submitted by outside institutions, were reviewed at a tertiary referral center (JHH) by at least one subspecialized expert genitourinary pathologist. Additional immunohistochemical (IHC) staining was performed or reviewed when available. IHC staining with adequate controls for chromogranin (catalog # 760-2519, clone: LK2H10; Ventana, Medical Systems, Inc. 1910 E. Innovation Park Drive Tucson, Arizona 85755, USA Indianapolis), synaptophysin (product code: NCL-L-SYNAP-299, clone: 27G12; Leica Biosystems Newcastle Ltd, Balliol Business Park Benton Lane Newcastle Upon Tyne NE12 8EW, United Kingdom), and Ki-67 (catalog # 790-4286, clone: 30-9; Ventana, Indianapolis) was performed on all cases following

Table 1 Demographic and pathologic features of the cohort.

Case #	Sex	Age (years)	Location	Specimen	Associated lesion	Ki-67	Outcome	Follow-up (months)
1	F	60	Left ureteral orifice	Biopsy	n/a	<1%	NED	137
2	M	45	Bladder	Biopsy	CCCG	1%	NED	128
3	M	58	Bladder	Biopsy	CCCG	1%	NED	86
4	M	59	Bladder	Biopsy	CCCG	1%	NED	84
5	M	56	Prostatic urethra	Biopsy	n/a	<1%	NED	82
6	F	72	Bladder	Biopsy	Urothelial papilloma	<1%	NED	66
7	M	73	Bladder	Biopsy	CCCG	2%	NED	37
8	F	64	Urethra	Biopsy	Florid vBn	5%	NED	72
9	F	69	Bladder	Biopsy	CCCG	1%	NED	62
10	M	54	Bladder neck	Polyp resection	n/a	2%	NED	61

Abbreviations: CCCG, chronic cystitis cystica et glandularis; n/a, not available; vBn, von Brunn's nest; NED, No evidence of disease.

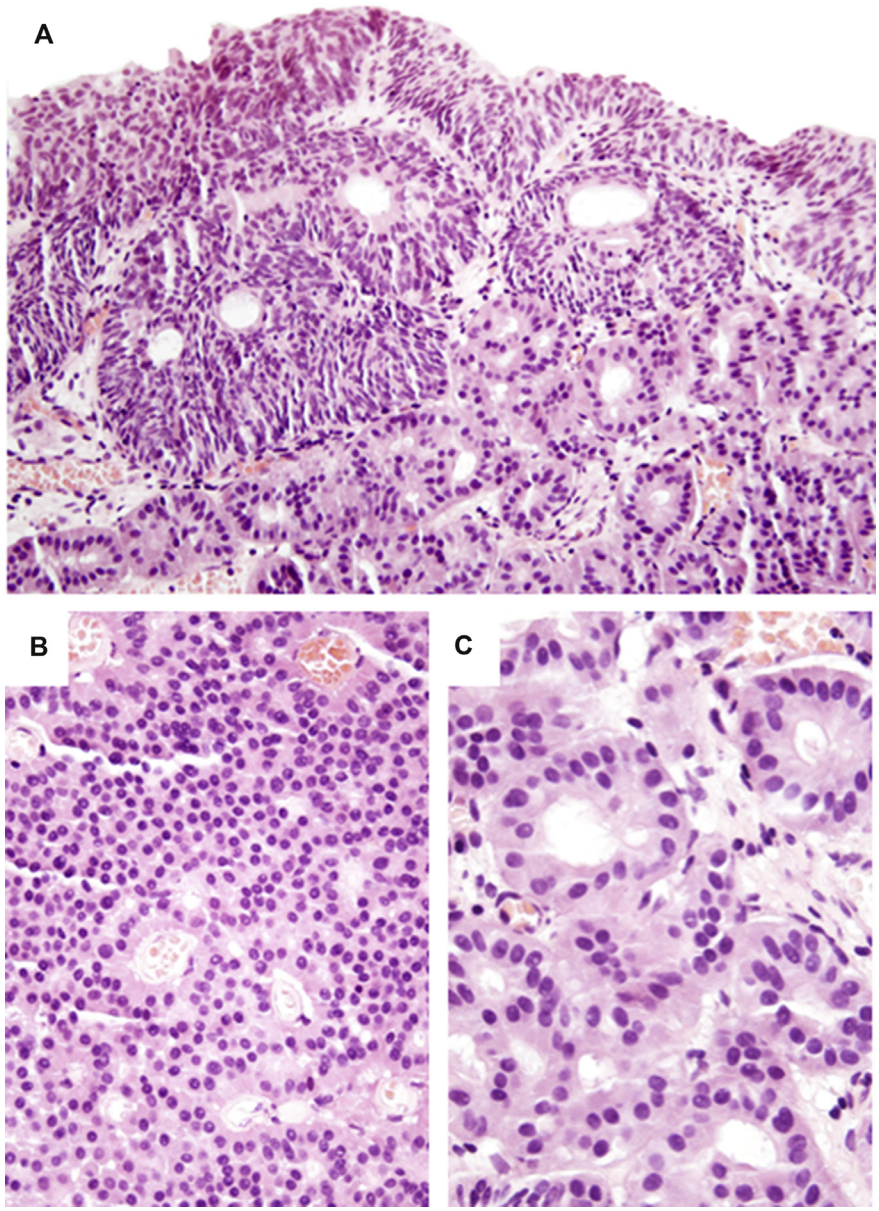

Fig. 1 A, Low-magnification (×10) view of a hematoxylin and eosin staining of a WD-NET with characteristic pseudoglandular architecture and overlying benign urothelium. B and C(×20,×40), On higher magnification, the uniform and nonatypical nuclei with stippled chromatin can be appreciated. WD-NET, well-differentiated neuroendocrine tumor.

standard manufacturer protocols. In addition, adjuvant staining was performed as needed (see supplementary Table 1).

3. Results

A total of 10 cases were identified. All consisted of consultations from other institutions. Patients included 6 men and 4 women, ranging from 45 to 73 (mean = 61) years of age. Specimens included 9 biopsies and 1 polyp resection. Size was available for 2 cases (1 and 4 mm). Seven cases arose in the bladder, with one located in the bladder neck; 1 arose in the prostatic urethra, 1 arose in the female urethra, and 1 arose in the left ureteral orifice. Table 1 summarizes all available demographic, pathologic, and outcome data for the cohort.

On microscopic examination, all lesions were confined to the lamina propria. Tumor architecture was pseudoglandular in all 10 cases, with one case showing purely cribriform, 1 showing purely acinar, and 1 showing mixed cribriform and acinar patterns. Associated cystitis cystica et glandularis (CCCG) was identified in 5 cases, and urothelial papilloma and florid Von Brunn's nests were identified in 2 additional cases. Tumor cells exhibited

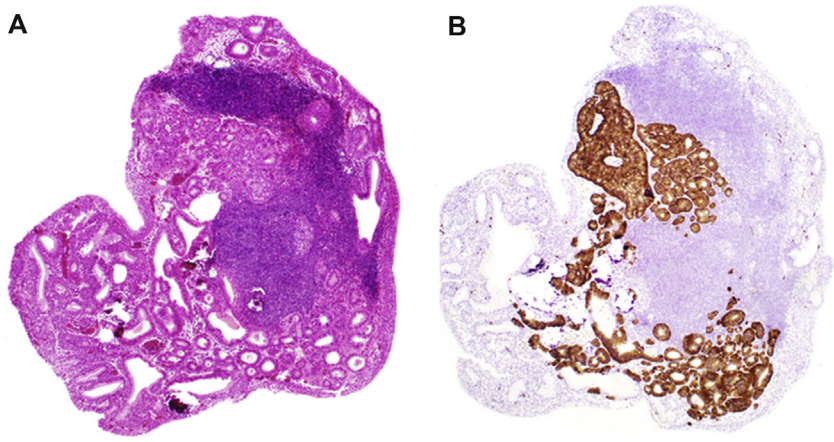

Fig. 2 Low-magnification (×10) views of an H&E-stained biopsy specimen with a conspicuous pseudoglandular lesion occupying the stroma (A) and highlighted neoplastic cells by immunohistochemical staining with synaptophysin (B). H&E, hematoxylin and eosin.

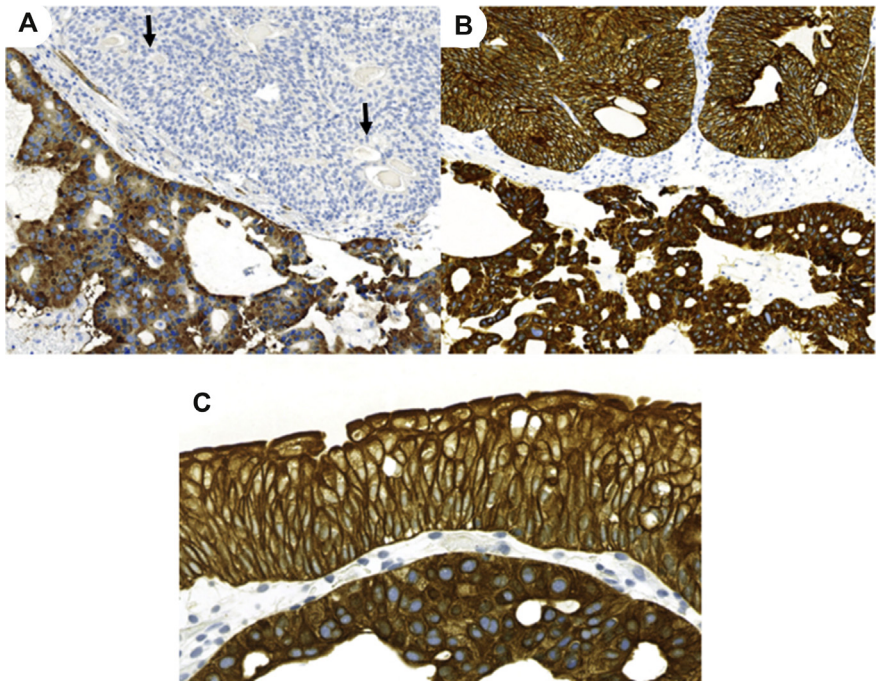

Fig. 3 Microphotographic composite showing a high-magnification microphotograph (×20) of immunohistochemical staining with synaptophysin and CK20. Notice the contrast between the synaptophysin-positive tumor cells and negative benign urothelium with features of florid cystitis cystica et glandularis (arrows) (A). Although CK20 highlights both the tumor and benign urothelium (B), the neoplastic cells at the bottom can be identified by the high nucleus-to-cytoplasm ratio and the coarse cytoplasmic pattern of staining (C) (×40).

typical features of WD-NET in other sites: uniform round to cuboidal cells, inconspicuous nuclei, and stippled chromatin (Fig. 1). No mitosis or necrosis was identified in any of the 10 cases.

IHC staining for synaptophysin (Fig. 2) and chromogranin was diffusely positive in all 10 cases, while CD56 was positive in 5, focal in 2, and negative in 3 cases. The Ki-67 proliferation index was 5% or less in all tumors. The differential diagnosis of prostate cancer was raised in 1 case, with prominent glandular architecture arising in the prostatic urethra. A cytokeratin cocktail IHC staining was positive (Fig. 3), while staining for prostate markers PSA, P501S, and PSMA was negative in tumor cells, ruling out prostatic origin and further confirming the diagnosis of WD-NET. In addition, in a case arising in the bladder neck, staining for PAX8, GATA3, NKX3.1, PSA, P501s, CDX2, P40, and CK20 was performed, and all markers were negative.

Follow-up ranged from 37 to 137 months (mean = 82; median = 77). There was no evidence of residual disease or recurrence in any of the 10 patients during the follow-up period.

4. Discussion

Our cohort of 10 LUT WD-NET cases represents the largest reported to date. With an extended median follow-up of up to 77 (mean = 82) months, no recurrence was detected in any of the cases, indicating a favorable biologic behavior. Similar to the study by Chen and Epstein [6], most patients in our cohort of WD-NET presented in the sixth or seventh decade of life, and men were more frequently affected. The 2 cases with available tumor size (1 and 4 mm) are in accordance with the previously described small size of less than 1 cm for WD-NETs.

WD-NETs of the genitourinary tract share cytologic and architectural features with counterparts in other anatomical sites. A wide variety of cellular architecture has been identified in the genitourinary tract. Romero et al. [18] described WD-NET of the kidney as having a mixture of trabecular, cord-like, nested, pseudoglandular, insular, rosette-like, and tubular patterns. Wang et al. [19] also described mixed patterns of growth including pseudoglandular and follicular patterns in 66% of primary testicular carcinoid tumors. Only 5 primary prostatic WD-NET cases have been described in the literature and have shown nested, trabecular, pseudoglandular, and sheet-like architecture [20–22]. Although pseudoglandular architecture is present in other Genitourinary (GU) sites, this architectural pattern seems to predominate in LUT WD-NET [6,10–17]. All 10 tumors in our cohort had pseudoglandular architecture including cribriform and acinar patterns. This tumoral architecture poses diagnostic challenges on small biopsies, namely, WD-NET can be overlooked when associated with adjacent CCCG or florid von Brunn's nests as seen in more than half of our cases. The pseudoglandular pattern of WD-NET can also mimic adenocarcinoma, mainly of prostatic, bladder, or colonic origin. Site-specific IHC markers such as NKX3.1, PSA, P501s; GATA3, and CDX2 can be of utility in resolving such differential diagnosis as demonstrated in two of our cases. Chen and Epstein [6] described positivity for prostate-specific acid phosphatase in bladder WD-NET. Therefore, using newer and more specific prostate markers is highly recommended. A high index of suspicion is necessary to avoid a misdiagnosis and inappropriate patient management.

Paraganglioma must be considered when faced with a tumor that exhibits NE features. Although also rare in the bladder, it is more frequent than WD-NET. Paraganglioma is characteristically composed of large polygonal cells with amphophilic to acidophilic cytoplasm and nuclei with hyperchromatic or smudged chromatin. The cells are arranged in a distinctive nested *zellballen* pattern separated by delicate vascular structures and fibrous septae. It can also present a diffuse growth pattern or pseudorosette formations. Similar to WD-NETs, mitosis and necrosis are rare [4,5]. Paragangliomas frequently involve the muscularis propria unlike most of the published WD-NET cases; all cases in our cohort were limited to the lamina propria. A single case report of WD-NET invading the muscle is on record by Baydar and Tasar [23]. Synaptophysin and chromogranin are not helpful in the differential of WD-NET and paraganglioma, given their shared expression in both tumors. S100 staining will highlight the sustentacular cells in paraganglioma, which can help distinguish the two entities [24], and cytokeratin positivity strongly favors WD-NET over paraganglioma [5,6].

The strengths of this study include expert review by subspecialized genitourinary pathologists in a single tertiary care institution and the extended length of follow-up, the longest published to date. Albeit small, the number of cases in this study is the largest published to date, as a single cohort, regarding this recognizably rare entity. The retroactive and consultative nature of the cohort could be seen as a weakness owing to the limitation of access to comprehensive clinical data.

In summary, we present the largest series of WD-NET of the LUT to date that includes the first cases of WD-NET arising in the ureteral orifice and female urethra and the third such case in the prostatic urethra. The outcome in our series supports a favorable long-term biologic behavior for WD-NET.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2020.11.014.

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