Neuroendocrine tumors of the prostate

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Neuroendocrine (NE) differentiation in tumors of the prostate or in the setting of prostate cancer (PCa) is rare. A survey of these lesions is presented, including usual PCa with focal NE marker-positive cells, Paneth cell-like change, prostatic ‘carcinoid’, high-grade NE carcinoma, as well as other tumors that do not fit neatly into these categories. The most significant clinical and pathologic features, emerging molecular evidence and the importance of differentiating NE tumors involving the prostate from secondary involvement are highlighted.

Modern Pathology (2018) 31, S122–S132; doi:10.1038/modpathol.2017.164

The current article is based upon a talk entitled “Neuroendocrine Tumors of the Prostate”, delivered at the 2017 United States and Canadian Academy of Pathology Annual Meeting Long Course. It is significant that this topic was allotted a talk of its own, as looking back to the last Prostate Long Course at USCAP 2003, prostatic neuroendocrine (NE) tumors—that is, small cell carcinoma (SmCC)—were subsumed within a talk regarding various unusual subtypes of prostate cancer (PCa). Although NE differentiation in the setting of PCa remains rare, more recent descriptions of various NE phenomena in PCa in the literature^{1–4} and as, if not more, significantly, an interest from the genitourinary oncology perspective, with the incidence of so-called “neuroendocrine prostate cancer” thought to be more common/rising in the setting of castrate-resistant (post-anti-androgen therapy) prostate cancer (CRPC),^{5–8} have warranted an update.

NE cells in normal prostatic tissue

First described by Pretl in 1944,⁹ focal NE cells are widely distributed in the prostate,^{10–11} are members of the diffuse APUD cell system¹² and are thought to arise, with prostatic secretory cells, from endodermal-derived pluripotent prostatic stem cells.¹³ Although their exact function is unknown, it is postulated that they are involved in prostatic growth and differentiation, as well as in homeostatic regulation of the secretory process.¹⁴ Their role may be mediated through their morphology, which

includes both flask-shaped “open” cells with apical processes extending to the lumen and “closed” cells, which interdigitate with normal secretory cells and contain long dendritic processes (Figure 1).¹⁴ On H&E staining, however, these cells are typically undetectable.

NE differentiation in prostatic tumors: proposed classifications

Over the past 5 years, with clinical and molecular data emerging from the study of PCa treated with modern androgen deprivation therapies,^{7–8} attempts to refine the terminology for NE lesions in the prostate and/or in the setting of PCa have been advanced. The two modern proposed classifications^{15,16} are summarized in Table 1. They are essentially similar, with the World Health Organization 2016 classification¹⁶ adopting the terminology “well-differentiated NE tumor (carcinoid)” used in other organs¹⁷ and viewing the category of “mixed NE carcinoma-acinar adenocarcinoma” from the Prostate Cancer Foundation meeting classification¹⁵ as subsets of cases within the “small cell” and “large cell” NE carcinoma categories. Although these classifications are an excellent framework, a number of issues persist: (a) on a practical level, the use of “neuroendocrine differentiation” in usual PCa or Paneth cell-like change is a potential source of confusion, as in undiscerning hands it may be still be interpreted as high-grade NE carcinoma; (b) there are a group of tumors discussed within the publications, but not well-represented within the tabular classifications, which show a range of morphology not typical for either high-grade acinar adenocarcinoma nor classic for small/large cell high-grade NE carcinoma and which show positivity for both prostatic and NE markers (often diffuse); (c) much of the NE PCa referred to in recent

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Received 31 July 2017; revised 12 September 2017; accepted 14 September 2017

publications⁷ in the setting of CRPC refers to patients who present with a constellation of clinical features, termed “small cell” or “anaplastic” by investigators, but for which the spectrum of pathologic findings is quite variable. The remainder of this article will review the range of NE manifestations, with practical suggestions about how to think about, identify, diagnose and study these lesions.

Prostatic adenocarcinoma with focal NE marker-positive cells

Thirty to 100% of primary conventional PCa contain scattered NE cells,^{18–20} mostly resembling other malignant prostatic secretory cells on light microscopy. This finding can be seen in both primary and metastatic sites. These cells can be focally detected by immunohistochemistry (IHC) with markers such as chromogranin and may also express prostatic markers such as prostatic-specific antigen (PSA),²⁰ indicating dual biologic potential. Whether focal NE marker-positive cells in PCa have prognostic import is controversial, with some early studies suggesting correlation between increasing numbers of chromogranin-positive cells and worse

Figure 1 Focal chromogranin immunoreactivity in benign prostatic glands; note the dendritic quality of the NE marker-positive cells.

prognosis.^{21–23} Conversely, most authors have correlated the extent of NE marker-positive cells with increasing tumor grade and failed to show an independent effect on survival.^{24–28} Hence, routine staining of PCa for NE IHC markers, in the absence of architectural/cytologic evidence suggestive of NE differentiation, is not recommended.

Similarly, there is evidence that metastatic PCa contains a population of NE marker-positive cells,²⁹ which do not express the androgen receptor (AR)^{30–32} and hence may not be suppressed by androgen ablation.²⁹ This had led to conjecture that NE cells possess the ability to “escape” usual hormonal therapy in advanced PCa, with some reports of increased NE marker-positive cells in CRPC, as well as possible prognostic significance.^{30,33} However, other reports argue that these relationships depend on the agent used in androgen deprivation and have demonstrated no statistical correlation between quantity of NE marker-positive cells and disease-specific survival.²⁷ These varying results suggest that the often limited and focal distribution of NE cells in PCa makes its difficult to study their relevance, especially in limited specimens, such as biopsies.³⁴ Although the true meaning of increased, focal NE marker-positive cells remains elusive, a number of studies have shown potential roles for these cells in PCa progression by paracrine growth stimulation of non-NE cells, inhibition of apoptosis and stimulation of neo-angiogenesis.^{29,33,35}

Prostatic adenocarcinoma with Paneth cell-like change

Occasionally NE cells with bland nuclei and coarse cytoplasmic eosinophilic granules are seen in a patchy manner in both normal and cancerous specimens, a phenomenon termed “Paneth cell-like” change, because of their superficial resemblance to Paneth cells in the GI tract.^{2,36} In reality, these cells are more akin to intestinal NE cells, which express NE markers and do not contain lysozyme, unlike true Paneth cells.³⁷ Paneth cell-like change may be seen across the spectrum of PCa grades, as well as in PCa previously treated with androgen deprivation/

Table 1 Existing Classifications of prostate cancer with neuroendocrine differentiation

<i>Prostate Cancer Foundation working committee proposed classification</i>	<i>2016 World Health Organization genitourinary tumor classification</i>
Usual prostate adenocarcinoma with NE differentiation	NE cells in usual prostate cancer
Adenocarcinoma with Paneth cell NE differentiation	Adenocarcinoma with Paneth cell-like NE differentiation
Carcinoid tumor	Well-differentiated NE tumor (carcinoid)
Small cell carcinoma	Small cell NE carcinoma
LCNEC	Large cell NE carcinoma
Mixed (small or large cell) NE carcinoma-acinar adenocarcinoma	

Abbreviations: LCNEC, large cell neuroendocrine carcinoma; NE, neuroendocrine.

Figure 2 (a) PCa cells with Paneth cell-like change intermixed with cancer displaying bubbly cytoplasm/pyknotic nuclei, indicating hormonal therapy effect; (b) Paneth cell-like change in cancer growing as cords/nests, mimicking pattern 5; (c) PCa showing extreme Paneth cell-like change admixed with usual carcinoma and (d) higher magnification from same tumor showing features that may mimic carcinoid, including pseudo-rosetting; diffuse chromogranin (e) and focal, yet discrete PSA (f) immunohistochemical labeling in the cancer focus depicted in c and d.

hormonal therapy (Figure 2a); these cells express both PSA and NE markers.

Unusually, these cells may be observed as single cells, cords or nests of tumor cells.² Such cases, as well as a more recently described variant, which lacks the coarse eosinophilic granules on H&E, but displays deeply amphophilic cytoplasm and NE markers positivity,⁴ may present a diagnostic dilemma, as grading them based on architecture would likely result in assigning Gleason pattern 5 (Figure 2b). Follow-up in small series,^{2,4} however, has suggested that these cases do not manifest clinical progression commensurate with a high-grade diagnosis and have outcome dependent on standard grading (in the non-Paneth cell-like areas) and staging parameters. It is suggested that only the conventional carcinoma be graded, to avoid inaccurate upgrading, and a notation made regarding this finding.² Consideration may be given in future classifications to reserving the verbiage of “neuroendocrine differentiation” for the high-grade NE carcinomas and high-grade PCa with diffuse NE marker positivity (an emerging group of tumors), rather than for more focal NE findings (ie, focal NE marker-positive cells or Paneth cell-like change), to avoid any confusion regarding clinical and therapeutic import.

Of additional note is a recent study of 25 PCa with varying degrees of Paneth cell-like change, which found that 45% showed amplification of the *Aurora Kinase A (AURKA)* gene, a regulator of mitosis/meiosis.³⁸ When comparing histologically similar cases with and without *AURKA* amplification, this alteration was associated with a higher percentage of Paneth cell-like cells and a higher overall Gleason score.³⁹ Although the true molecular and clinical meaning of these findings remains for future study, the high frequency of *AURKA* amplification and its potential prognostic significance are interesting avenues of inquiry, given that therapies targeting *AURKA* are being tested in the clinic.³⁹

Prostatic “carcinoid/well-differentiated neuroendocrine tumor”

A fair number of cases have been reported as “prostatic carcinoid tumors”.^{40–45} However, as usual PCa may exhibit focal NE differentiation, distinguishing carcinoid-like adenocarcinomas from a true primary prostatic carcinoid may be challenging.⁴⁰ Especially in architecturally high-grade tumors, these entities may share nested and microacinar/“rosette-like” patterns of growth with nuclear uniformity, prostate-specific acid phosphatase positivity, and immunohistochemical/ultrastructural evidence of NE differentiation.^{46,47} Furthermore, cellular aggregates with variably interspersed eosinophilic NE granules, that is, Paneth cell-like change, may also convey an impression of carcinoid tumor.² (Figures 2c-f). A careful read of the literature

shows that outside those occurring in young patients with multiple endocrine neoplasia syndromes,^{48,49} nearly all “prostatic carcinoids” are actually PCa with “carcinoid-like” morphologic features^{50,51} and in fact, most of these cases exhibit PSA and NE marker labeling, as well as admixed usual acinar adenocarcinoma. To be labeled a true prostatic carcinoid—akin to the well-differentiated NE tumors in other organs¹⁷—tumors must exhibit typical carcinoid architecture and cytology, PSA negativity and absence of admixed adenocarcinoma. Using these guidelines, this diagnosis should be rarely, if ever, made and its inclusion within future classifications should be considered carefully.

High-grade NE carcinoma

High-grade NE carcinoma of the prostate or in setting of PCa is rare, largely occurs in the form of SmCC⁵² and is thought to represent between 1 and 5% of all prostatic malignancies when mixed adenocarcinoma and SmCC cases are included.¹¹ Although high-grade NE carcinoma can arise *de novo*, it is most typically seen in the setting of prior anti-androgen therapy. Nonetheless, older data from a rapid autopsy program indicates that morphologically high-grade NE carcinomas evolve in only about 10% of PCa patients treated with hormonal therapy who develop CRPC.⁵³ Conversely, in the constellation of extrapulmonary SmCC, the prostate is a relatively common site.⁵⁴ The majority of prostatic SmCC lack clinically evident hormone production, with only rare reports of ectopic adrenocorticotrophic or antidiuretic hormone secretion.⁵⁵

High-grade NE carcinoma of prostate histologically resembles the spectrum of SmCC and large cell NE carcinoma (LCNEC) described at other sites,^{1,3,56,57} ranging from “classic” SmCC features as seen in the lung, that is, diffuse sheets of round blue hyperchromatic cells exhibiting nuclear molding, granular chromatin, inconspicuous nucleoli, scant cytoplasm and frequent mitoses/apoptotic debris (Figures 3a and b) to lesions with a LCNEC phenotype, including “organoid”, trabecular or palisaded architecture, associated geographic necrosis and large cells with more abundant cytoplasm and macronucleoli. These tumors are most often associated with Ki-67/MiB-1 proliferation rates of $\geq 50\%$.

Approximately 50% of high-grade NE carcinomas are composite tumors with conventional PCa.¹¹ These are the so-called “mixed” NE carcinoma-acinar adenocarcinomas¹⁵ and almost invariably show abrupt transitions between the acinar and NE components (Figures 3c-f), which may be differentially highlighted using IHC markers, yet may show common *TP53* gene mutation in both components, suggesting a common clonal origin.⁵⁸ Loss of *RB1* gene by deletion is a common event in prostatic SmCC, which may be detected in these lesions and ~50% of concurrent acinar PCa by loss of Rb IHC

Figure 3 (a) SmCC on prostatic needle biopsy—cells with little cytoplasm growing in sheets and (b) higher magnification displaying nuclear molding and high mitotic and apoptotic rates. (c) Mixed adenocarcinoma-high-grade NE carcinoma in a radical prostatectomy showing abrupt transition between the two components with (d) chromogranin staining highlighting the small cell component; metastases from tumor depicted in c, left pelvic lymph node (e) showing adenocarcinoma and right pelvic lymph node (f) showing high-grade NE histology.

expression, compared with a very low % of otherwise high-grade acinar PCa.⁵⁹ Diagnostically, the high-grade NE carcinoma component of these tumors should not be assigned a Gleason grade. Owing to their respective features, classic SmCC is more readily differentiated from diffuse growth of Gleason pattern 5 PCa than LCNEC, which may share cytoplasmic (more abundant/amphophilic) and nucleolar features.¹ Uncommonly, acinar carcinoma will become admixed with cells, clusters and/or nests of cells that retain nucleoli but have architectural and cytoplasmic features and proliferation rates consistent with NE carcinoma.

A number of studies have reported the immunophenotype of SmCC and conventional PCa.^{60–62} Overall, they have found strong labeling for PSA in most PCa, with at least focal expression in approximately 25% of SmCC, as well as diffuse NE marker labeling in SmCC with substantially less staining in usual PCa.^{61,62} Furthermore, although most have maintained that malignant NE cells within high-grade NE carcinoma do not express AR,^{30,31} this finding is not universal; focal AR positivity may be detected.⁶² The presence of morphologically mixed prostatic acinar adenocarcinoma in many high-grade NE carcinomas, coupled with evidence of cells that may co-express PSA/PAP/AR and NE markers^{1,56,61,62} suggests evolution of a subset of multipotent non-NE prostatic tumor cells as the derivation for prostatic high-grade NEC,^{1,13,24,61,63} a phenomenon more recently termed “transdifferentiation”.⁶⁴

Given the relative rarity of high-grade NE carcinoma in the setting of PCa, the main differential diagnosis is with non-prostatic high-grade NE carcinoma such as metastasis from the lung. From an anatomic perspective, direct extension from a NE carcinoma of the bladder is significantly more likely and may share morphologic and immunohistochemical features, including TTF-1 positivity.^{62,65} A clinical scenario in which this dilemma arises is in transurethral resection specimens from the bladder/bladder neck. Although the presence of non-invasive or unequivocal invasive urothelial carcinoma should certainly discourage a diagnosis of high-grade NE carcinoma of prostatic origin, detection of TMPRSS2-ERG rearrangement⁶⁶ may be an important marker indicating prostatic origin in difficult cases, in combination with urothelial-specific markers.

Early studies of prostatic SmCC found TMPRSS2-ERG rearrangement rates of 70–85%, findings thought to indicate that rearrangement was associated with aggressive disease.^{67–69} Subsequent studies, however, revealed an incidence of approximately 45%, a similar rate to that seen in conventional primary PCa.^{70,71} Multiple reports have demonstrated that in nearly all cases, there is concordant ERG rearrangement status between concurrent usual PCa and SmCC components, indicating

common clonal origin and re-emphasizing the notion of divergent differentiation for these tumors.^{70,71}

Usually, TMPRSS2-ERG rearrangement brings ERG under androgen-regulated transcription control and hence, ERG protein expression detected by IHC shows excellent correlation (~90%) with rearrangement status. Lotan *et al*⁷⁰ highlight cases of SmCC in the setting of PCa, which are no longer reliant on androgen signaling (AR negative). In this scenario, ERG protein expression by IHC may not correlate with rearrangement status and similarly PSA and NKX3.1, an androgen-regulated transcription factor, may show negative IHC labeling. This idea is echoed in a report from an autopsy series cohort, which studied the correlation of ERG IHC with fluorescent *in situ* hybridization (FISH) rearrangement status in CRPC.⁷² They found that tumors that are no longer androgen dependent, but have ERG rearrangement, may be completely negative (or show only focal, weak positivity) for ERG IHC. Hence, FISH and not IHC is the best way to test for ERG rearrangement in SmCC/high-grade NE carcinoma cases suspected for prostatic origin. Importantly, all cases of SmCC of bladder and lung origin that have been investigated have been negative for ERG rearrangement, highlighting the utility of this marker, when detected, in some cases.^{68–70}

Comparable to other sites, prostatic high-grade NE carcinoma present at advanced stage, are often unresectable and display a high frequency of visceral metastases and abysmal survival.^{56,73,74} Small modern series have suggested managing prostatic SmCC with a combination of androgen deprivation and cisplatin-based therapies followed by consolidative surgery or radiotherapy.^{73–75} However, even chemotherapy-treated patients tend to progress rapidly. Few examples of distinct prostatic LCNEC have been reported,^{1,76–78} with the majority being incidental findings in palliative transurethral resection specimens in patients with CRPC.¹ Reported cases have been detected late in the disease course, with widespread metastases to bone and viscera, uniformly poor responses to NE-specific chemotherapy and limited survival.¹

Prostatic carcinoma with diffuse NE differentiation

There is a group of tumors that do not fit cleanly into proposed classification schemes for NE differentiation in PCa and comprise an unknown percentage of primary/metastatic lesions without systematic clinical follow up. Importantly, these mostly high-grade tumors share the common feature of labeling for prostatic markers such as AR/PSA/NKX3.1, although also displaying diffuse (or non-focal, confluent) NE marker IHC expression. Moreover, when reported, these tumors are most often seen in patients with a prior history of anti-androgen therapy.^{15,79,80} These cancers show morphologic variability, from tumors

Figure 4 PCa with diffuse NE differentiation. (a) Lymph node biopsy from a patient with PCa treated with androgen deprivation therapy demonstrating sheet-like/diffuse growth of tumor cells and (b) higher magnification displaying features not typically seen in SmCC, including ample cytoplasm and macronucleoli; note some cells showing bubbly cytoplasm consistent with therapeutic effect; immunohistochemical stains showing strong, diffuse labeling for prostatic markers, PSA (c) and NKX3.1 (d), and NEs, chromogranin (e) and synaptophysin (f).

composed of nests and ribbons of tumor cells +/- rosette-like architecture with amphophilic cytoplasm, "salt and pepper" chromatin and central prominent nucleoli (mimicking carcinoid), to cases with sheet-like growth with rare lumen formation, yet displaying more cytoplasm and more prominent nucleoli than typically seen in SmCC (Figures 4a-f), to tumors with solid/nested architecture, no discernible gland formation and cells with amphophilic cytoplasm variable nuclear pleomorphism, one to several macronucleoli and brisk mitotic activity, yet lacking the peripheral palisading and necrosis classic for LCNEC. Although the literature is limited, it is plausible (and even likely) that some of these tumors have been classified into established categories—"carcinoid"/SmCC/LCNEC—in the past. Recent attempts to name these tumors have yielded terms such as "prostate cancer with overlapping features of small cell and acinar adenocarcinoma"¹⁵ to describe tumors with one cell population in which it is difficult to determine whether to diagnose SmCC (because of diffuse architecture) or Gleason pattern 5 PCa (because of cytology). Another group has proposed the term "amphicrine carcinoma"⁷⁹ for high-grade lesions with cytology, but not architecture, of classic LCNEC and expressing both exocrine (prostatic) and NE markers.⁸¹ As large series of these cases are not yet available and nuances in morphology, grading, clinical presentation and molecular alterations remain to be studied, one may suggest reporting this group of tumors diagnostically as "prostatic carcinoma with diffuse NE differentiation" with a descriptive note to separate them from more focal NE findings, as well as from well-established categories of high-grade NE carcinoma.

CRPC with aggressive clinical presentation

Oncologists have focused on a group of PCas with a highly aggressive clinical course, which they have variably referred to as: "anaplastic", "small cell" and "treatment-related NE prostate cancer".^{7,8} These designations are not based on the morphology or immunoprofile of these tumors, but rather on a spectrum of clinical features distinct from those seen in aggressive usual PCa. These features include: visceral and lytic (rather than blastic) bony metastases, bulky lymph node metastases in the pelvic region, low PSA at presentation despite bulky disease (pre-hormonal therapy or at symptomatic progression in the castrate setting) and short interval to CRPC after initiation of hormonal therapy. High serum chromogranin, LDH, CEA and/or malignant hypercalcemia have also been reported.⁷ From the molecular perspective, the Weill-Cornell group has demonstrated concurrent *AURKA* and *N-MYC* gene amplifications in ~70% of a cohort of hormone naïve PCa specimens, which clinically progressed to "aggressive CRPC" (as defined above) and similar

or higher percentage of these molecular alterations in specimens from "aggressive CRPC" or metastases, compared with only 5% in an unselected PCa cohort.⁸² The true incidence of this clinical syndrome is not known, but with greater utilization of potent anti-androgen agents, such as abiraterone and enzalutamide,^{83,84} and increasing commonality of biopsy from metastatic sites, one may anticipate that more specimens from such cases will come to attention. From a diagnostic perspective, it is within the realm of possibility that these cases could show morphology of pure or mixed SmCC/high-grade NE carcinoma, usual high-grade PCa or what we have termed "prostatic carcinoma with diffuse NE differentiation",⁸⁵ distinctions that await further study.

In sum, the present article has reviewed the well-established entities in the spectrum of NE lesions of the prostate/in the setting of PCa, although highlighting the morphologic variation within those categories, which may characterize new or emerging subsets of tumors. Pathologists should exercise caution in reporting tumors with NE differentiation, making clear whether the findings are amongst the focal phenomena or those that are associated with high-grade features. Hopefully, further refinement of the morphologic classification of NE lesions in the setting of PCa over the coming years will engender better correlation among emerging molecular findings, sensitivity to therapy and clinical outcomes.

Disclosure/conflict of interest

The author declares no conflict of interest.

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